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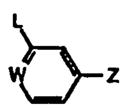
(54) Title: TRI-SUBSTITUTED PHENYL DERIVATIVES USEFUL AS PDE IV INHIBITORS



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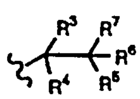

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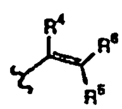

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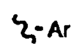

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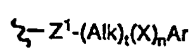

(D)

(57) Abstract

Compounds of general formula (1) are described, formula wherein =W- is (1) =C(Y)- where Y is a halogen atom, or an alkyl or $-XR^a$ group where X is -O-, $-S(O)_m-$ [where m is zero or an integer of value 1 or 2], or $-N(R^b)-$ [where R^b is a hydrogen atom or an optionally substituted alkyl group] and R^a is a hydrogen atom or an optionally substituted alkyl group or, (2) =N-; L is (1) a $-C(R)=C(R^1)(R^2)$ or $[-CH(R)]_nCH(R^1)(R^2)$ group; is (2) a $-(X^a)_nAlk'Ar'$, or $Alk'X^aAr'$ group; or is (3) X^aR^1; Z is a group (A), (B), (C) or (D) wherein Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; Z^1 is a group $-NR^{12}C(O)-$ [where R^{12} is a hydrogen atom or an optionally substituted alkyl or $(Alk)_tAr$ group], $-C(O)NR^{12}-$, $-NR^{12}C(S)-$, $-C(S)NR^{12}-$, $-C\equiv C-$, $-NR^{12}SO_2-$, or $-SO_2NR^{12}-$; Alk is an optionally substituted straight or branched alkyl chain optionally interrupted by an atom or group X; t is zero or an integer of value 1, 2 or 3; R^3 is a hydrogen or a fluorine atom or an optionally substituted straight or branched alkyl group or an OR^{11} group [where R^{11} is a hydrogen atom or an optionally substituted alkyl, alkenyl, alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group]; R^4 is a hydrogen atom or an optionally substituted alkyl, $-CO_2R^8$, $-CSNR^9R^{10}$, -CN, $-CH_2CN$, or $-(CH_2)_tAr$ group where t is zero or an integer of value 1, 2 or 3 and Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; provided that when L is a group of type (2) or (3) above, then Z is a group of type (A) or type (B) in which R^4 is a $-(CH_2)_tAr$ group; R^5 is a group $-(CH_2)_tAr$; R^6 is a hydrogen or a fluorine atom, or an optionally substituted alkyl or $-CO_2R^8$, $-CONR^9R^{10}$, $-CSNR^9R^{10}$, -CN or $-CH_2CN$ group; R^7 is a hydrogen or a fluorine atom, an optionally substituted straight or branched alkyl group, or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group; and the salts, solvates, hydrates, prodrugs and N-oxides thereof. Compounds according to the invention are phosphodiesterase type IV inhibitors and are useful in the prophylaxis and treatment of disease such as asthma where unwanted inflammatory response or muscular spasm is present.

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TRI-SUBSTITUTED PHENYL DERIVATIVES USEFUL AS PDE IV INHIBITORS

This invention relates to a novel series of tri-substituted phenyl derivatives, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

Many hormones and neurotransmitters modulate tissue function by elevating intra-cellular levels of adenosine 3', 5'-cyclic monophosphate (cAMP). The cellular levels of cAMP are regulated by mechanisms which control synthesis and breakdown. The synthesis of cAMP is controlled by adenyl cyclase which may be directly activated by agents such as forskolin or indirectly activated by the binding of specific agonists to cell surface receptors which are coupled to adenyl cyclase. The breakdown of cAMP is controlled by a family of phosphodiesterase (PDE) isoenzymes, which also control the breakdown of guanosine 3',5'-cyclic monophosphate (cGMP). To date, seven members of the family have been described (PDE I-VII) the distribution of which varies from tissue to tissue. This suggests that specific inhibitors of PDE isoenzymes could achieve differential elevation of cAMP in different tissues, [for reviews of PDE distribution, structure, function and regulation, see Beavo & Reifsnyder (1990) TIPS, 11: 150-155 and Nicholson et al (1991) TIPS, 12: 19-27].

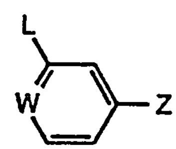
There is clear evidence that elevation of cAMP in inflammatory leukocytes leads to inhibition of their activation. Furthermore, elevation of cAMP in airway smooth muscle has a spasmolytic effect. In these tissues, PDE IV plays a major role in the hydrolysis of cAMP. It can be expected, therefore, that selective inhibitors of PDE IV would have therapeutic effects in inflammatory diseases such as asthma, by achieving both anti-inflammatory and bronchodilator effects.

The design of PDE IV inhibitors has met with limited success to date, in that many of the potential PDE IV inhibitors which have been synthesised have lacked potency and/or have been capable of inhibiting more than one type of PDE isoenzyme in a non-selective manner. Lack of a selective

action has been a particular problem given the widespread role of cAMP *in vivo* and what is needed are potent selective PDE IV inhibitors with an inhibitory action against PDE IV and little or no action against other PDE isoenzymes.

We have now found a novel series of tri-substituted phenyl derivatives, members of which are potent inhibitors of PDE IV at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. These compounds inhibit the human recombinant PDE IV enzyme and also elevate cAMP in isolated leukocytes. The compounds of the invention are therefore of use in medicine, especially in the prophylaxis and treatment of asthma.

Thus according to one aspect of the invention, we provide a compound of formula (1)



(1)

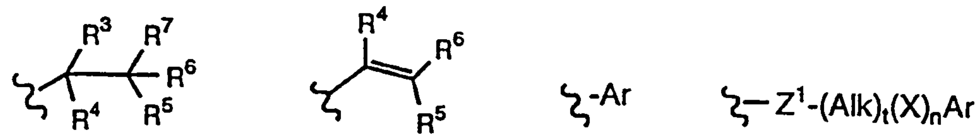
wherein

=W- is (1) =C(Y)- where Y is a halogen atom, or an alkyl or $-XR^a$ group where X is -O-, $-S(O)_m-$ [where m is zero or an integer of value 1 or 2], or $-N(R^b)-$ [where R^b is a hydrogen atom or an optionally substituted alkyl group] and R^a is a hydrogen atom or an optionally substituted alkyl group or, (2) =N-;

L is (1) a $-C(R)=C(R^1)(R^2)$ or $[-CH(R)]_nCH(R^1)(R^2)$ group where R is a hydrogen or a fluorine atom or a methyl group, and R^1 and R^2, which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, $-CO_2R^8$ [where R^8 is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group], $-CONR^9R^{10}$ [where R^9 and R^{10}, which may be the same or different are defined for R^8], $-CSNR^9R^{10}$, -CN or $-NO_2$ group, or R^1 and R^2, together with the C atom to which they are attached are linked to form an optionally substituted cycloalkyl, cycloalkenyl or heterocycloaliphatic

group and n is zero or the integer 1; or is (2) $-(X^a)_nAlk'Ar'$, or $-Alk'X^aAr'$ where X^a is a group X, Ar' is an optionally substituted heterocycloaliphatic, or an optionally substituted monocylic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms, Alk' is an optionally substituted straight or branched alkylene, alkenylene or alkynylene chain optionally interrupted by one or more L^1 atoms or groups [where L^1 is a linker atom or group] and n is zero or the integer 1; or is (3) X^aR' where R' is Ar' or is an optionally substituted polycycloalkyl or polycycloalkenyl group optionally containing one or more -O-, or -S- atoms or $-N(R^b)-$ groups;

Z is a group (A), (B), (C) or (D):



(A), (B), (C), or (D)

wherein

Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

Z^1 is a group $-NR^{12}C(O)-$ [where R^{12} is a hydrogen atom or an optionally substituted alkyl or $(Alk)_tAr$ group], $-C(O)NR^{12}-$, $-NR^{12}C(S)-$, $-C(S)NR^{12}-$, $-C{\equiv}C-$, $-NR^{12}SO_2-$, or $-SO_2NR^{12}-$;

Alk is an optionally substituted straight or branched alkyl chain optionally interrupted by an atom or group X;

t is zero or an integer of value 1, 2 or 3;

R^3 is a hydrogen or a fluorine atom or an optionally substituted straight or branched alkyl group or an OR^{11} group [where R^{11} is a hydrogen atom or an optionally substituted alkyl, alkenyl, alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group];

R^4 is a hydrogen atom or an optionally substituted alkyl, $-CO_2R^8$, $-CSNR^9R^{10}$, -CN, $-CH_2CN$, or $-(CH_2)_tAr$ group where t is zero or an integer of value 1, 2 or 3 and Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms, provided that when L is a group of type (2) or

(3) above then Z is a group of type (A) or type (B) in which R^4 is a $-(CH_2)_tAr$ group;
R^5 is a group $-(CH_2)_tAr$;
R^6 is a hydrogen or a fluorine atom, or an optionally substituted alkyl or $-CO_2R^8$, $-CONR^9R^{10}$, $-CSNR^9R^{10}$, -CN or $-CH_2CN$ group;
R^7 is a hydrogen or a fluorine atom, an optionally substituted straight or branched alkyl group, or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group; and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

It will be appreciated that certain compounds of formula (1) may have one or more chiral centres, depending on the nature of the groups Alk, R^1, R^2, R^3, R^4, R^5, R^6 and R^7. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates.

Compounds of formula (1) in which L is a $-C(R)=C(R^1)(R^2)$ group and/or Z is the group (B), may exist as geometric isomers depending on the nature of the groups R, R^1, R^2, R^4, R^5 and R^6, and the invention is to be understood to extend to all such isomers and mixtures thereof.

In the compounds of formula (1), when =W- is =C(Y)- and Y is a halogen atom Y may be for example a fluorine, chlorine, bromine or iodine atom.

When W in the compounds of formula (1) is a group =C(Y)- and Y is $-XR^a$, R^a may be, for example, a hydrogen atom or an optionally substituted straight or branched alkyl group, for example, an optionally substituted C_{1-6}alkyl group, such as a methyl, ethyl, n-propyl or i-propyl group. Optional substituents which may be present on R^a groups include one or more halogen atoms, e.g. fluorine, or chlorine atoms. Particular R^a groups include for example $-CH_2F$, $-CH_2Cl$, $-CHF_2$, $-CHCl_2$, $-CF_3$ or $-CCl_3$ groups.

When =W- in the compounds of formula (1) is a group =C(Y)- where -Y is $-N(R^b)$, =W- may be a $=C(NH_2)-$, $=C(NHCH_3)-$ or $=C(NHC_2H_5)-$ group.

In compounds of formula (1), X may be an oxygen or a sulphur atom, or a group -S(O)-, $-S(O)_2-$, -NH- or C_{1-6} alkylamino, for example a C_{1-3} alkylamino, e.g. methylamino [$-N(CH_3)-$] or ethylamino [$-N(C_2H_5)-$] group.

Alkyl groups represented by Y, R^1, R^2 or R^b in the compounds of formula (1) include optionally substituted straight or branched C_{1-6} alkyl groups optionally interrupted by one or more X atoms or groups. Particular examples include C_{1-3} alkyl groups such as methyl, ethyl, n-propyl or i-propyl groups. Optional substituents on these groups include one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl or C_{1-6} alkoxy e.g. C_{1-3} alkoxy such as methoxy or ethoxy or $-CO_2R^8$, $-CONR^9R^{10}$, $-CSNR^9R^{11}$ or -CN groups. Particular substituted alkyl groups include for example $-CH_2F$, $-CH_2Cl$, $-CHF_2$, $CHCl_2$, $-CH_3$ or $-CCl_3$ groups.

Alkenyl groups represented by R^1 or R^2 in the compounds of formula (1) include optionally substituted straight or branched C_{2-6}alkenyl groups optionally interrupted by one or more X atoms or groups. Particular examples include ethenyl, propen-1-yl and 2-methylpropen-1-yl groups. Optional substituents include those described above in relation to alkyl groups represented by the groups R^1 or R^2.

Alkynyl groups represented by R^1 or R^2 in compounds of formula (1) include optionally substituted straight or branched C_{2-6}alkynyl groups optionally interrupted by one or more X atoms or groups. Particular examples include ethynyl and propyn-1-yl groups. Optional substituents include those described above in relation to alkyl groups represented by the groups R^1 or R^2.

When R^1 or R^2 in compounds of formula (1) is an alkoxy or alkylthio group it may be for example an optionally substituted C_{1-6}alkoxy or C_{1-6}alkylthio group optionally interrupted by one or more X atoms or groups. Particular examples include C_{1-3}alkoxy, e.g. methoxy or ethoxy, or C_{1-3}alkylthio e.g. methylthio or ethylthio groups. Optional substituents include those described above in relation to alkyl groups represented by the groups R^1 or R^2.

When R^1 and R^2 together with the carbon atom to which they are attached in the compounds of formula (1) are linked to form a cycloalkyl or cycloalkenyl group, the group may be for example a C_{3-8}cycloalkyl group such as a cyclobutyl, cyclopentyl or cyclohexyl group or a C_{3-8} cycloalkenyl group containing for example one or two double bonds such as a 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-cyclohexadien-1-yl or 3,5-cyclohexadien-1-yl group, each cycloalkyl or cycloalkenyl group being optionally substituted by one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, straight or branched C_{1-6}alkyl e.g. C_{1-3}alkyl such as methyl or ethyl, hydroxyl or C_{1-6}alkoxy e.g. C_{1-3}alkoxy such as methoxy or ethoxy groups.

The linker atoms represented by the group L^1 include for example -O- or -S- atoms. Particular groups represented by the linker group L^1 are -S(O)-, $-S(O)_2-$, $-N(R^b)-$, -C(O)-, $-C(O)_2-$, -C(S)-, $-C(NR^b)-$ $-CON(R^b)-$, $-CSN(R^b)-$, $-N(R^b)CO-$, $-N(R^b)CS-$, $-SON(R^b)-$, $-SO_2N(R^b)-$, $-N(R^b)SO-$, $-N(R^b)SO_2-$, $-N(R^b)SO_2N(R^b)-$, $-N(R^b)SON(R^b)-$, $-N(R^b)CON(R^b)-$ or $-N(R^b)CSN(R^b)-$ groups. It will be appreciated that when the chain Alk is interrupted by two or more L^1 atoms or groups, such atoms or groups may be adjacent to one another, for example to form a group $-N(R^b)-C(NR^b)-N(R^b)-$ or -O-CONH-.

When L is a $-(X^a)_n$Alk'Ar' or Alk'X^aAr' group where Alk' is an alkylene chain L may be for example an optionally substituted straight or branched C_{1-8}alkylene chain optionally interrupted by one or more L^1 linker atoms or groups. Particular examples include $-CH_2Ar'$, $-(CH_2)_2Ar'$, -OAr', -SAr', $-N(R^b)Ar'$, -C(O)Ar', -C(S)Ar', $-CON(R^b)Ar'$, $-CSN(R^b)Ar'$, -SOAr', $-SON(R^b)Ar'$, $-SO_2Ar'$, $-SO_2N(R^b)Ar'$, OCH_2Ar', $-SCH_2Ar'$, $-N(R^b)CH_2Ar'$, $-CH_2OAr'$, $-CH_2SAr'$, $-CH_2N(R^b)Ar'$, $-CH_2C(O)Ar'$, $-CH_2C(S)Ar'$, $-CH_2CON(R^b)Ar'$, $-CH_2CSN(R^b)Ar'$, $-CH_2SOAr'$, $-CH_2SO_2Ar'$, $-(CH_2)_2OCH_2Ar'$, $-(CH_2)_2SCH_2Ar'$, $-(CH_2)_2SOCH_2Ar'$, $-(CH_2)_2SO_2CH_2Ar'$, $-(CH_2)_3Ar'$, $-O(CH_2)_3Ar'$, $-S(CH_2)_3Ar'$, $-N(R^b)(CH_2)_3Ar'$, $-SO(CH_2)_3Ar'$, $-SO_2(CH_2)_3Ar'$, $-(CH_2)_3OAr'$, $-(CH_2)_3SAr'$, $-(CH_2)_3N(R^b)Ar'$, $-(CH_2)_3SOAr'$ or $-(CH_2)_3SO_2Ar'$ group. Optional substituents on these groups include

those mentioned above in relation to the alkyl groups represented by Y, R^1, R^2 or R^b.

When L is a -$(X^a)_n$Alk'Ar' or Alk'X^aAr' group where Alk' is an alkenylene chain it may be an optionally substituted straight or branched mono or polyunsaturated C_{2-8}alkenylene chain optionally interrupted by one or more L^1 linker atoms or groups. Particular examples include -(CH=CH)Ar', -CH=CH-CH_2Ar', -CH_2-CH=CHAr', -CH=CH-CH_2Ar', -CH_2-CH=CHAr', -OCH=CH-CH_2Ar', -OCH_2-CH=CHAr', -SCH=CH-CH_2Ar', -SCH_2-CH=CHAr', -N(R^b)CH=CH-CH_2Ar', -CH=CH-CH_2-OAr', -CH_2-CH=CH_2-OAr' or -CH=CH-CH=CHAr' group. Optional substituents on these groups include those mentioned above in relation to the alkyl groups represented by Y, R^1, R^2 or R^b.

When L is a $(X^a)_n$Alk'Ar' or Alk'X^aAr' group where Alk' is an alkynylene chain, it may be an optionally substituted straight or branched mono or polyunsaturated C_{2-8}alkynylene chain optionally interrupted by one or more L^1 linker atoms or groups. Particular examples include -C≡CAr', -C≡C-CH_2Ar', -CH_2-C≡C-Ar', -OC≡C-CH_2Ar', -OCH_2-C≡CAr', -SC≡C-CH_2Ar', -SCH_2-C≡CAr', -N(R^b)C≡C-CH_2Ar', -N(R^b)CH_2-C≡CAr', -C≡C-CH_2OAr', -CH_2-C≡COAr', -C≡C-CH_2SAr', -CH_2-C≡CSAr', -CH_2-C≡CN(R^b)Ar' or -C≡C-CH_2N(R^b)Ar' group. Optional substituents on these groups include those mentioned above in relation to the alkyl groups represented by Y, R^1, R^2 or R^b.

When R^1 and R^2, together with the C atom to which they are attached are linked to form an optionally substituted heterocycloaliphatic group, and/or when Ar' is a heterocycloaliphatic group, the group may be for example an optionally substituted C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl group containing one or more -O-, or -S- atoms, or -N(R^b)- groups such as a pyrrolidinyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolidinyl, pyrazolidinyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, 3-pyrrolinyl, 2-imidazolinyl, or 2-pyrazolinyl group. Optional substituents which may be present on such groups include one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, straight or branched C_{1-6} alkyl e.g. C_{1-3} alkyl

such as methyl or ethyl, hydroxyl or C_{1-6} alkoxy e.g. C_{1-3} alkoxy such as methoxy or ethoxy groups.

Polycycloalkyl groups represented by R' in compounds of formula (1) include optionally substituted C_{6-10} polycycloalkyl, e.g. bicycloalkyl or tricycloalkyl groups optionally containing one, two or more -O- or -S- atoms or $-N(R^b)-$ groups. Polycycloalkenyl groups represented by Ar' include optionally substituted C_{6-10} polycycloalkenyl, e.g. bicycloalkenyl or tricycloalkenyl groups optionally containing one, two or more -O- or -S- atoms or $-N(R^b)$ groups. The degree of unsaturation of polycycloalkenyl groups may be varied widely and the term is to be understood to include groups with one, two, three or more -CH=CH- groups. Optional substituents which may be present on such groups include those mentioned above in relation to the Ar' group when Ar' is a heterocycloaliphatic group.

When the group R^7 in compounds of formula (1) is an OR^c group it may be for example a hydroxyl group; or a group $-OR^c$ where R^c is an optionally substituted straight or branched C_{1-6}alkyl group, e.g. a C_{1-3}alkyl group such as a methyl or ethyl group, a C_{2-6}alkenyl group such as an ethenyl or 2-propen-1-yl group, a C_{1-3}alkoxyC_{1-3}alkyl group such as a methoxymethyl, ethoxymethyl or ethoxyethyl group, a C_{1-6}alkanoyl, e.g. C_{1-3}alkanoyl group such as an acetyl group, or a formyl [HC(O)-], carboxamido ($CONR^{13}R^{13a}$) or thiocarboxamido ($CSNR^{13}R^{13a}$) group, where R^{13} and R^{13a} in each instance may be the same or different and is each a hydrogen atom or an optionally substituted straight or branched C_{1-6}alkyl, e.g. C_{1-3}alkyl group such as methyl or ethyl group. Optional substituents which may be present on such R^c, R^{13} or R^{13a} groups include those described below in relation to the alkyl groups R^3, R^4, R^6, R^7 and R^{12}.

Alkyl groups represented by R^3, R^4, R^6, R^7 or R^{12} in compounds of formula (1) include optionally substituted straight or branched C_{1-6} alkyl groups, e.g. C_{1-3} alkyl groups such as methyl, ethyl, n-propyl or i-propyl groups. Optional substituents which may be present on these groups include one or more halogen atoms, e.g. fluorine, chlorine, bromine or

iodine atoms, or hydroxyl or C_{1-6}alkoxy e.g. C_{1-3}alkoxy such as methoxy or ethoxy groups.

When R^1, R^2, R^4 or R^6 is a $-CO_2R^8$, $-CONR^9R^{10}$ or $CSNR^9R^{10}$ group it may be for example a $-CO_2H$, $-CONH_2$ or $-CSNH_2$ group or a group $-CO_2R^8$, $-CONR^9R^{10}$, $-CSNR^9R^{10}$, $-CONHR^{10}$, or $-CSNHR^{10}$ where R^8, R^9 and R^{10} where present is a C_{1-3}alkyl group such as methyl or ethyl group, a C_{6-12}aryl group, for example an optionally substituted phenyl, or a 1- or 2- naphthyl group, or a C_{6-12}aryl C_{1-3}alkyl group such as an optionally substituted benzyl or phenethyl group. Optional substituents which may be present on these aryl groups include R^{14} substituents discussed below in relation to the group Ar.

When the chain Alk is present in compounds of formula (1) it may be an optionally subtituted straight or branched C_{1-3}alkylene chain optionally interrupted by an atom or group X. Particular examples include $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2OCH_2-$, $-CH_2SCH_2-$, or $-CH_2N(R^b)CH_2$, e.g. $-CH_2NHCH_2-$ or $-CH_2N(CH_3)CH_2-$ chains. Optional substituents include those described in relation to the alkyl groups represented by R^3, R^4, R^6, R^7 and R^{12}.

In the compounds of formula (1) when the group $-(Alk)_t(X)_nAr$ is present it may be a group -Ar, $-CH_2Ar$, $-(CH_2)_2Ar$, $-(CH_2)_3Ar$, $-CH_2OAr$, $-CH_2OCH_2Ar$, $-CH_2N(R^b)Ar$ or $-CH_2N(R^b)CH_2Ar$ group.

Monocyclic or bicyclic aryl groups represented by the group Ar, Ar', or R' in compounds of formula (1) include for example C_{6-12} optionally substituted aryl groups, for example optionally substituted phenyl, 1–or 2–naphthyl, indenyl or isoindenyl groups.

When the monocyclic or bicyclic aryl group Ar, Ar' or R' contains one or more heteroatoms it may be for example a C_{5-10} optionally substituted heteroaryl group containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, Ar heteroaryl groups may be for example monocyclic or bicyclic heteroaryl groups. Monocyclic heteroaryl groups include for example five- or six-

membered heteroaryl groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaryl groups include for example nine- or ten- membered heteroaryl groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Examples of heteroaryl groups represented by Ar, Ar' or R' include pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl. Example of bicyclic heteroaryl groups include quinolinyl or isoquinolinyl groups.

The heteroaryl group represented by Ar, Ar' or R' may be attached to the remainder of the molecule of formula (1) through any ring carbon or heteroatom as appropriate. Thus, for example, when the group Ar or Ar' is a pyridyl group it may be a 2-pyridyl, 3-pyridyl or 4-pyridyl group. When it is a thienyl group it may be a 2-thienyl or 3-thienyl group, and, similarly, when it is a furyl group it may be a 2-furyl or 3-furyl group. In another example, when the group Ar is a quinolinyl group it may be a 2-, 3-, 4-, 5-, 6-, 7- or 8- quinolinyl and when it is an isoquinolinyl, it may be a 1-, 3-, 4-, 5-, 6-, 7- or 8- isoquinolinyl group.

When in compounds of formula (1) the Ar, Ar' or R' group is a nitrogen-containing heterocycle it may be possible to form quaternary salts, for example N-alkyl quaternary salts and the invention is to be understood to extend to such salts. Thus for example when the group Ar is a pyridyl group, pyridinium salts may be formed, for example N-alkylpyridinium salts such as N-methylpyridinium.

The aryl or heteroaryl groups represented by Ar, Ar' or R', in compounds of formula (1) may each optionally be substituted by one, two, three or more substituents [R^{14}]. The substituent R^{14} may be selected from an atom or group R^{15} or $-Alk^1(R^{15})_m$ wherein R^{15} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, cycloalkoxy, cycloaliphatic, formyl [HC(O)-], carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, -C(O)R" [where R" is a group Alk^1 where Alk^1 is a straight or branched C_{1-6} alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene chain optionally interrupted by one, two, or three -O-, or -S- atoms or $-S(O)_z-$, (where z is an integer 1 or 2) or $-N(R^b)-$ groups; or is a group Ar" (where Ar" is as defined for Ar), $-SO_3H$, $-SO_2R"$, $-SO_2NH_2$, $-SO_2NHR"$ $-SO_2N[R"]_2$, $-CONH_2$, -CONHR" -CON[R"]$_2$, $-NHSO_2H$, $-N(R")SO_2H$, $-NHSO_2R"$, $-NR"SO_2R"$, $-N[SO_2R"]_2$, $-NHSO_2NH_2$, $-NR"SO_2NH_2$, $-NHSO_2NHR"$, $-NR"SO_2NHR"$, $-NHSO_2N[R"]_2$, $-N(R")SO_2N[R"]_2$, -NHC(O)R", -NR"C(O)R", -N[C(O)R"]$_2$, -NHC(O)H, -NR"C(O)H, -NHC(O)OR", -NR"C(O)OR", -NHC(O)OH, -NR"C(O)OH, $-NHCONH_2$, -NHCONHR", -NHCON[R"]$_2$, -NR"CON[R"]$_2$, -C(S)R", $-C(S)NH_2$, -C(S)NHR", -C(S)N[R"]$_2$, -NHC(S)R", -NR"C(S)R", -N[[C(S)R"]$_2$, -NHC(S)H, -NR"C(S)H, $-NHC(S)NH_2$, -NHC(S)NHR", -NHC(S)N[R"]$_2$, -NR"C(S)N[R"]$_2$, -Ar" or -XAr" group; and m is zero or an integer 1, 2 or 3 .

When in the group $-Alk^1(R^{15})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{15} may be present on any suitable carbon atom in $-Alk^1$. Where more than one R^{15} substituent is present these may be the same or different and may be present on the same or different carbon atom in Alk^1. Clearly, when m is zero and no substituent R^{15} is present or when Alk^1 forms part of a group such as $-SO_2Alk^1$ the alkylene, alkenylene or alkynylene chain represented by Alk^1 becomes an alkyl, alkenyl or alkynyl group.

When R^{15} is a substituted amino group it may be a group $-NH[Alk^1(R^{15a})_m]$ [where Alk^1 and m are as defined above and R^{15a} is as defined above for R^{15} but is not a substituted amino, a substituted hydroxyl or a substituted thiol group] or a group $-N[Alk^1(R^{15a})_m]_2$ wherein each $-Alk^1(R^{15a})_m$ group is the same or different.

When R^{15} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{15} is a cycloalkoxy group it may be for example a C_{5-7}cycloalkoxy group such as a cyclopentyloxy or cyclohexyloxy group.

When R^{15} is a substituted hydroxyl or substituted thiol group it may be a group $-OAlk^1(R^{15a})_m$ or $-SAlk^1(R^{15a})_m$ respectively, where Alk^1, R^{15a} and m are as just defined.

Esterified carboxyl groups represented by the group R^{15} include groups of formula $-CO_2Alk^2$ wherein Alk^2 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12}arylC_{1-8}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxy-propyl group. Optional substituents present on the Alk^2 group include R^{14} substituents described above.

When the group R^{15} in compounds of formulae (1) and (2) is an optionally substituted C_{3-9}cycloaliphatic group, it may be a C_{3-9}cycloalkyl or C_{3-9}cycloalkenyl group such as a C_{5-7}cycloalkyl or C_{5-7}cycloalkenyl group, containing 1, 2, 3 or more heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particular examples of such R^{15} groups include pyrrolyl, e.g. 2H-pyrrolyl, pyrrolinyl, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, 3H-pyrrolyl, 2H-imidazolyl, dithiolyl, e.g. 1, 2- or 1,3-dithiolyl,

oxathiolyl, e.g. 3H-1-2 or 1,3-oxathiolyl, 5H-1,2,5-oxathiozolyl, 1,3-dioxinyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 1,4-2H-1,2- or 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. -o- or p- isoxazinyl, oxathiazinyl, e.g. 1,2,5-, 1,2,6-oxathiazinyl, 1,3,5,2-oxadiazinyl, or 1,2,4-diazepinyl groups. Optional substituents which may be present on such groups include those substituents discussed above in relation to the group Ar' where Ar' is a heterocycloaliphatic group.

It will be appreciated that the group Ar, Ar' or R' may be attached to the remainder of the molecule of formula (1) through either a ring carbon atom or heteroatom.

Particular examples of the group Alk^1 when present include methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S- atoms or -S(O)-, $-S(O)_2-$ or $-N(R^b)-$ groups.

Particularly useful atoms or groups represented by R^{14} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6} hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C_{1-6}alkylthiol e.g. methylthiol or ethylthiol, C_{1-6}alkoxy, e.g. methoxy or ethoxy, C_{5-7}cycloalkyl e.g. cyclopentyl, C_{5-7} cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, C_{1-6} alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^2$ [where Alk^2 is as defined above], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylamino-

carbonyl, phenylaminocarbonyl, sulphonylamino ($-NHSO_2H$), C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6} dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino ($-NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl or C_{1-6} alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino, thiocarboxamido ($-CSNH_2$), C_{1-6} alkylaminothiocarbonyl, e.g. methylaminothiocarbonyl or ethylaminothiocarbonyl, C_{1-6}dialkylaminothiocarbonyl, e.g. dimethylaminothiocarbonyl or diethylaminothiocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6} dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino, or diethylaminothiocarbonylamino, aminocarbonylC_{1-6}alkylamino, e.g. aminocarbonylmethylamino or aminocarbonylethylamino, aminothiocarbonylC_{1-6}alkylamino e.g. aminothiocarbonylmethylamino or aminothiocarbonylethylamino, formylaminoC_{1-6} alkylsulphonylamino, e.g. formylaminomethylsulphonylamino or formylaminoethylsulphonylamino, thioformylaminoC_{1-6}alkylsulphonylamino, e.g. thioformylaminomethylsulphonylamino or thioformylethylsulphonylamino, C_{1-6}acylaminosulphonylamino, e.g. acetylaminosulphonylamino, C_{1-6}thioacylaminosulphonylamino, e.g. thioacetylaminosulphonylamino groups, -Ar", e.g. phenyl, -XAr" e.g. phenoxy, or $-Alk^1Ar"$ e.g. benzyl or phenethyl groups.

Where desired, two R^{14} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{2-6}alkylenedioxy group such as ethylenedioxy.

It will be appreciated that where two or more R^{14} substituents are present, these need not necessarily be the same atoms and/or groups. The R^{14}

substituents may be present at any ring carbon atom away from that attached to the rest of the molecule of formula (1). Thus, for example, in phenyl groups represented by Ar any substituent may be present at the 2-, 3-, 4-, 5- or 6- positions relative to the ring carbon atom attached to the remainder of the molecule.

Particular examples of the chain Z^1 in compounds of formula (1) include -NHCO-, -CONH-, -NHCS-, -CSNH-, $-NHSO_2-$, $-SO_2NH-$ and -C=C-.

In the compounds of formula (1), when an ester group is present, for example a group $-CO_2R^8$ or $-CO_2Alk^2$ this may advantageously be a metabolically labile ester.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Prodrugs of compounds of formula (1) include those compounds, for example esters, alcohols or aminos, which are convertible *in vivo* by metabolic means, e.g. by hydrolysis, reduction, oxidation or trans-esterification, to compounds of formula (1).

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

In the compounds of formula (1) the group =W- is preferably a =C(Y)- group. In compounds of this type Y is preferably a $-XR^a$ group where X is -O- and R^a is an optionally substituted ethyl group or, especially, an optionally substituted methyl group. Especially useful substituents which may be present on R^a groups include one, two or three fluorine or chlorine atoms.

The group L in compounds of formula (1) is preferably a $-CH=C(R^1)(R^2)$ group. In compounds of this type R^1 and R^2 are preferably linked together with the C atom to which they are attached to form an optionally substituted cycloalkyl or cycloalkenyl group, especially a substituted cyclopentyl or cyclohexyl or, especially, a cyclopentyl or cyclohexyl group.

In the compounds of formula (1) where Z is the group (A), one preferred group of compounds are those where the group R^3 is a hydrogen atom; the group R^6 is a methyl group, or especially a hydrogen atom; the group R^7 is a methyl group, or especially a hydrogen atom; and R^4 and R^5 are as defined for formula (1). In compounds of this type R^6 and R^7 in one preference, is each a methyl group; in another preference, one of R^6 or R^7 is a methyl group and the other is a hydrogen atom, in general, however, R^6 and R^7 is each especially a hydrogen atom.

The groups R^4 and R^5 when present in compounds of formula (1) are each, independently, preferably a $-CH_2Ar$ group, or, especially, an -Ar group. Particularly useful R^4 or R^5 groups of this type include those groups in which Ar is a monocyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur, or, in particular, nitrogen atoms, and optionally substituted by one, two, three or more R^{14} substituents. In these compounds, when the group represented by Ar is a heteroaryl group it is preferably a nitrogen-containing monocyclic heteroaryl group, especially a six-membered nitrogen-containing heteroaryl group. Thus, in one preferred example, the groups R^4 and R^5

may each be a six-membered nitrogen-containing heteroaryl group. In another preferred example R^4 may be a monocyclic aryl group or a monocyclic or bicyclic heteroaryl group containing one or more oxygen, sulphur or nitrogen atom and R^5 may be a six-membered nitrogen-containing heteroaryl group. In these examples, the six-membered nitrogen-containing heteroaryl group may be an optionally substituted pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or imidazolyl group. Particular examples include optionally substituted 2-pyridyl, 3-pyridyl, 5-imidazolyl, or, especially, 4-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl or 3-pyrazinyl. The monocyclic aryl group may be a phenyl group or a substituted phenyl group, and the monocyclic or bicyclic heteroaryl group containing one or more oxygen, sulphur or nitrogen atom may be an optionally substituted 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 2-benzo(b)thiophenyl, 2-benzo(b)furyl or 4-isoquinolinyl group.

One particularly useful group of compounds of formula (1) when Z is a group (A) or (B) is that wherein R^4 and R^5 is each a pyridyl or, especially, a monosubstituted pyridyl, or preferably a disubstituted pyridyl group, or R^4 is a phenyl, thienyl or furyl, or substituted phenyl, thienyl or furyl group and R^5 is a pyridyl or, especially a monosubstituted pyridyl, or preferably a disubstituted pyridyl group.

In this particular group of compounds and also in general in compounds of formula (1) when R^4 and/or R^5 is a substituted phenyl group it may be for example a mono-, di- or trisubstituted phenyl group in which the substituent is an atom or group R^{14} as defined above. When the R^4 and/or R^5 group is a monosubstituted phenyl group the substituent may be in the 2-, or preferably 3-, or especially 4-position relative to the ring carbon atom attached to the remainder of the molecule. When the R^4 and/or R^5 group is a disubstituted phenyl group, the substituents may be in the 2,6 position relative to the ring carbon atom attached to the remainder of the molecule.

When in compounds of formula (1) R^4 and/or R^5 is a substituted pyridyl group it may be for example a mono-or disubstituted pyridyl group, such

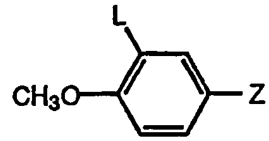
as a mono- or disubstituted 2-pyridyl, 3-pyridyl or especially 4-pyridyl group substituted by one or two atoms or groups R^{14} as defined above, in particular one or two halogen atoms such as fluorine or chlorine atoms, or methyl, methoxy, hydroxyl or nitro groups. Particularly useful pyridyl groups of these types are 3-monosubstituted-4-pyridyl or 3,5-disubstituted-4-pyridyl, or 2- or 4-monosubstituted-3-pyridyl or 2,4-disubstituted-3-pyridyl groups.

Other particularly useful groups of compounds of formula (1) where Z is the group (B), include those where R^4 is a $-CH_3$ group or a hydrogen atom; R^5 is a hydrogen atom, a -CN or a $-CH_3$ group; R^6 is as just described for R^4 and R^5 in the compounds of formula (1) where Z is the group (A).

Another particularly useful group of compounds of formula (1) when Z is a group (C) is that wherein Ar is a phenyl, naphthyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl, 5,6,7,8-tetrahydroquinolinyl or 5,6,7,8-tetrahydro-isoquinolinyl group. In compounds of this type when Ar is a quinolinyl group it may be for example a mono- or disubstituted quinolinyl group such as a 2-monosubstituted-4-quinolinyl group; when it is a pyridyl group, it may be an optionally substituted 3- or 4- pyridyl, e.g. a 2,3,5,6-tetrasubstituted-4-pyridyl or 2,4,6-trisubstituted-3-pyridyl group; when it is a pyrimidinyl group, it may be for example a 5-pyrimidinyl group or a 2-substituted 5-pyrimidinyl group; and when it is an isoquinolinyl group, it may be a 4-isoquinolinyl group.

Other especially useful groups of compounds of formula (1) include those where Z is a group (D) in which (1) $-Z^1-$ is a $-C(O)NR^{12}-$ group, where R^{12} is a hydrogen atom. In compounds of this type, t is preferably zero and Ar is a 2-nitrophenyl or 4-(3,5-dichloro)pyridyl group, or (2) those where $-Z^1-$ is a $-NR^{12}C(O)-$ group, where R^{12} is a hydrogen atom, t is zero and Ar is a 4-pyridyl or 4-(3,5-dichloro)pyridyl, benzyl or 2-methylbenzoate group, or t is an integer of value 1 and Ar is a 2- or 3-nitrophenyl, phenyl or 2-methylphenyl group.

A particularly useful group of compounds of formula (1) has the formula (2):



(2)

where (1) -L is a $-CH{=}C(R^1)(R^2)$ or $-CH_2CH(R^1)(R^2)$ group where R^1 and R^2 are linked together with the carbon atom to which they are attached to form a cycloalkyl group; or (2) L is a group -OAlkAr' where Alk is a C_{1-6}alkylene chain and Ar' is a monocyclic aryl or heteroaryl group. Particular examples of such L groups include benzyloxy, thienyloxy or phenyl-pentyloxy groups; or (3) L is a group OR' where R' is an optionally substituted polycycloalkyl or polycycloalkenyl group or is as described above for Ar'. Preferred examples of such R' groups include optionally substituted bicycylo[2.2.1]heptyl or bicyclo[2.2.1]heptenyl group. In particular R' is a bicyclo[2.2.1]hept-2-yl group; and Z is as defined for formula (1); and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

In compounds of formula (2) where R^3, R^6 or R^7 is present it is each preferably a hydrogen atom.

A particularly useful group of compounds according to the invention has the formula (2) wherein L is a OR' group and Z is the group (A). In this particular group of compounds R^3, R^6 and R^7 is each a hydrogen atom and R^4 and R^5 are as defined for compounds of formula (1) and the salts, solvates, hydrates and N-oxides thereof. Compounds of this type in which R' is a bicyclo [2.2.1] heptyl, particularly a bicyclo [2.2.1] hept-2-yl group are particularly useful. In this group of compounds, R^4 is preferably a monocyclic aryl group, particularly a phenyl or substituted phenyl group or R^4 is a six-membered nitrogen-containing monocyclic heteroaryl group, particularly a pyridyl or substituted pyridyl group and R^5 is a six-membered nitrogen-containing monocyclic heteroaryl group, especially a pyridyl or substituted pyridyl group, in particular a 4-pyridyl or substituted 4-pyridyl group.

Other particularly useful groups of compounds of formulae (1) or (2) where L is a group $-C(R)=C(R^1)(R^2)$ or $-(X^a)_nAlk'Ar'$ and Z is the group (B), include those where R^4 is a $-CH_3$ group or a hydrogen atom; R^5 is a hydrogen atom, a -CN or a $-CH_3$ group; R^6 is as just described for R^4 and R^5 in the compounds of formulae (1) or (2) where Z is the group (A).

Particular compounds according to the invention are:
(2R)-4-{2-[3-((2RS)-exo-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-2-phenylethyl}pyridine;
(±)-4-[2-(3-Benzyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine;
(±)-4-{2-[4-Methoxy-3-(3-thienyloxy)phenyl]-2-phenylethyl}pyridine;
(±)-4-[2-(3-Cyclopentylidenyl-4-methoxyphenyl)-2-phenylethyl]pyridine;
(±)-4-[2-(3-Cyclohexylidenyl-4-methoxyphenyl)-2-phenylethyl]pyridine;
(E, Z)-3-(3-Cyclopentylidenyl-4-methoxyphenyl)-2-(2,6-dichlorophenyl) propenenitrile;
(E, Z)-3-(3-Cyclopentylidenyl-4-methoxyphenyl)-2-(2,6-difluorophenyl) propenenitrile;
(E, Z)-4-[2-(3-Cyclopentylidenyl-4-methoxyphenyl)ethenyl]-3,5-dichloropyridine;
3-(3-Cyclopentylidenyl-4-methoxyphenyl)pyridine;
5-(3-Cyclopentylidenyl-4-methoxyphenyl)pyrimidine;
4-(3-Cyclopentylidenyl-4-methoxyphenyl)nitrobenzene;
3-(3-Cyclopentylmethyl-4-methoxyphenyl)pyridine;
N-(3-Cyclopentylidenyl-4-methoxyphenyl)-3,5-dichloro-4-pyridenecarboxamide;
4-[2-(3-Cyclopentylidenyl-4-methoxyphenyl)ethyl]pyridine;
N-{4-[2-(3-Cyclopentylidenyl-4-methoxyphenyl)ethyl]-3-pyridyl}phenylsulphonamide;
3-Cyclopentylidenyl-4-methoxy-N-(2-nitrobenzoyl)aniline;
N-(3-Cyclopentylidenyl-4-methoxyphenyl)-4-pyridinecarboxamide;
N-Phenyl-3-cyclopentylidenyl-4-methoxybenzamide;
N-(2-Nitrophenyl)-3-cyclopentylidenyl-4-methoxybenzamide;
N-(3,5-Dichloropyrid-4-yl)-3-cyclopentylidenyl-4-methoxybenzamide;
and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

Compounds according to the invention are selective and potent inhibitors of PDE IV. The ability of the compounds to act in this way may be simply determined by the tests described in the Examples hereinafter.

Particular uses to which the compounds of the invention may be put include the prophylaxis and treatment of asthma, especially inflamed lung associated with asthma, cystic fibrosis, or in the treatment of inflammatory airway disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign and malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis and artherosclerosis.

Compounds of the invention may also suppress neurogenic inflammation through elevation of cAMP in sensory neurones. They are, therefore, analgesic, anti-tussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

Compounds according to the invention may also elevate cAMP in lymphocytes and thereby suppress unwanted lymphocyte activation in immune-based diseases such as rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease.

Compounds according to the invention may also reduce gastric acid secretion and therefore can be used to treat conditions associated with hypersecretion.

Compounds of the invention may suppress cytokine synthesis by inflammatory cells in response to immune or infectious stimulation. They are, therefore, useful in the treatment of bacterial, fungal or viral induced sepsis and septic shock in which cytokines such as tumour necrosis factor (TNF) are key mediators. Also compounds of the invention may suppress inflammation and pyrexia due to cytokines and are, therefore, useful in the treatment of inflammation and cytokine-mediated chronic tissue

degeneration which occurs in diseases such as rheumatoid or osteo-arthritis.

Over-production of cytokines such as TNF in bacterial, fungal or viral infections or in diseases such as cancer, leads to cachexia and muscle wasting. Compounds of the invention may ameliorate these symptoms with a consequent enhancement of quality of life.

Compounds of the invention may also elevate cAMP in certain areas of the brain and thereby counteract depression and memory impairment.

Compounds of the invention may suppress cell proliferation in certain tumour cells and can be used, therefore, to prevent tumour growth and invasion of normal tissues.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution

with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formulae (1) and (2) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formulae (1) and (2) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

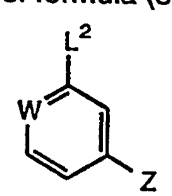
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the

active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular inflammatory condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg, e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds according to the invention may be prepared by the following processes. The symbols W, L, Z, X,R^1, R^2, R^3, R^4, R^5, R^6, and R^7 when used in the formulae below are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio, carboxy or aldehyde groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis" John Wiley and Sons, 1981].

Thus, according to a further aspect of the invention, compounds of general formula (1) where L is $X^aAlk'Ar'$, $Alk'X^aAr'$ or X^aR' may be prepared by coupling an intermediate of formula (3)



(3)

a) where L^2 is a group $-X^aH$ with a reagent $L^3Alk'Ar'$, or L^3R' where L^3 is a leaving group; or

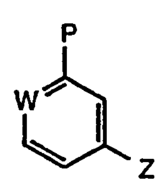
b) where L^2 is a group $-Alk'L^3$ with a reagent $Ar'X^aH$.

Leaving groups represented by L^3 include halogen atoms such as iodine, chlorine or bromine atoms, sulphonyloxy groups such as arylsulpyhonyl-oxy groups, e.g. p-toluenesulphonyloxy or hydroxyl groups.

The coupling reaction may be carried out in the presence of a base, e.g. an inorganic base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide, such as dimethylformamide or an ether, e.g. diethylether or a cyclic ether such as tetrahydrofuran or halogenated solvents, such as dichloromethane. The temperature of the reaction mixture may vary from ambient temperature or above, e.g. around 40°C to the reflux temperature. Where necessary, an activator may be used, such as diethyl-, diisopropyl-, or dimethylazodicarboxylate, in the presence of a phosphine, such as triphenylphosphine and a base, such as an amine, e.g. triethylamine.

Intermediates of formula (3) where L^2 is a group -Alk'L^3 wherein L^3 is a halogen atom may be prepared by reaction of an intermediate of formula (3) wherein Alk'L^3 is a -Alk'OH group with a halogenating agent, such as an inorganic acid halide e.g. thienylchloride, or an anhydride such as an arylsulphonic anhydride, e.g. p.toluenesulphonic anhydride, using conventional procedures.

Intermediates of formula (3) where L^2 is a group -X^aH may be prepared by deprotection of a protected compound of formula (4)

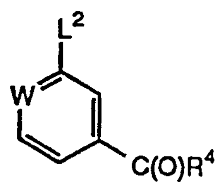


(4)

where P is a hydroxy, thio, or amino protecting group. Examples of hydroxy protecting groups include, for example ether groups, such as a cyclopentyloxy group. The deprotection reaction may take place in an

aqueous solvent, such as an aqueous ether, e.g. dioxane-water, in the presence of an acid, e.g. sulphuric acid at an elevated temperature. .g. around 90°C. Another example of protecting group P include t-butyldimethylsilyloxy group which can be cleaved by treatment with tetrabutylammonium fluoride to regenerate the free hydroxy group.

Intermediates of formula (3) where Z is a group (A) in which R^3 is a hydroxyl group and R^7 is a hydrogen atom may be prepared by reacting a ketone of formula (5)



(5)

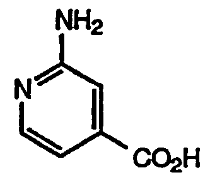
with an organometallic reagent R^5R^6 CHM, where M is a metal atom.

Metal atoms represented by Z include, for example, a lithium atom.

The reaction may be performed in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, at a low temperature e.g. around -70°C to ambient temperature. This reaction is particularly suitable for the preparation of compounds of formula (3) wherein R^5 is an electron deficient group such as a 2- or 4-pyridyl group.

Reagents R^5R^6CHM are either known compounds or may be prepared, preferably *in situ* during the above process, by reaction of a compound $AlkCH_2M$ [where Alk is an alkyl group such as n-propyl] with a compound $R^5R^6CH_2$ where necessary in the presence of a base such as an amine e.g. diisopropylamine using the above-mentioned conditions.

Intermediates of formula (5) where L^2 is a group $-X^aH$ in which $-X^a$ is -NH-and R^4 is a hydrogen atom may be prepared from the known compound of formula (6)

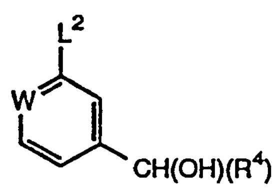


(6)

by reduction with a reducing agent, such as a lithium aluminium hydride, to give the alcohol derivative. This in turn may be oxidised, for example with manganese dioxide to afford an aldehyde of formula (5).

Intermediates of formula (3) where Z is a group (A) in which R^3 is a hydroxyl group may be prepared by reacting a ketone of formula (5) with a reagent $R^5CHR^6R^7$ using a base, such as an organometallic base, for example an organolithium reagent e.g. n-butyllithium, in a solvent, such as an ether, e.g. tetrahydrofuran, at around -70°C to room temperature.

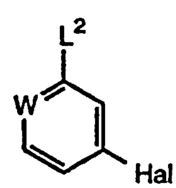
Ketones of formula (5) may be prepared by oxidation of an alcohol of formula (7)



(7)

using an oxidising agent, such as manganese (IV) oxide, in a solvent, such as dichloromethane, at room temperature.

Alternatively, ketones of formula (5) may be prepared by reaction of a halide of formula (8)



(8)

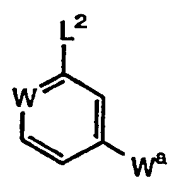
[where Hal is a halogen atom such as a bromine or chlorine atom] by halogen-metal exchange with a base such as n-butyllithium followed by reaction with a nitrile R^4CN, an acid chloride R^4COCl or an ester R^4CO_2A (where A is an alkyl group, e.g. a methyl group), in a solvent such as tetrahydrofuran at a low temperature, e.g. around -70°C, and subsequent treatment with an acid such as hydrochloric acid at e.g. -20°C to ambient temperature.

Alcohols of formula (7) may be prepared

(1) by reacting a halide of formula (8) e.g. a bromide, with an aldehyde R^4CHO, in the presence of a base, such as n-butyllithium, in a solvent, e.g. tetrahydrofuran, at a temperature from around -70°C to room temperature; or

(2) by reacting an aldehyde of formula (9) where W^a is a -CHO group (as described hereinbelow) with an organometallic compound, such as an organolithium R^4Li, or a Grignard R^4MgBr, in a solvent, such as tetrahydrofuran, at a low temperature, e.g. around -55°C to 0°C.

Intermediates of formula (3) where Z is a group (B) may be prepared by condensing an intermediate of formula (9)



(9)

where

(a) W^a is a $-C(O)R^4$ group wherein R^4 is as defined for formula (1) but is not a -CN or $-CH_2CN$ group, with a compound $R^5CH_2R^6$; or where

(b) W^a is a $-CH_2R^4$ group with an aldehyde or ketone R^5COR^6 where R^5 is as just defined for R^4; or where

(c) W^a is a $-C(O)R^4$ group with a silane derivative $(Alk^a)_3SiCH(R^5)(R^6)$, where Alk^a is an alkyl group; in each instance in the presence of a base or an acid in a suitable solvent.

Bases for use in these reactions include inorganic bases, for example alkali and alkaline earth metal bases, e.g. hydroxides, such as sodium or potassium hydroxide; alkoxides, for example sodium ethoxide; organic bases, for example amines such as piperidine; and organolithium bases, such as alkyllithium, e.g. n-butyllithium bases. Suitable solvents include alcohols such as ethanol, or ethers such as tetrahydrofuran. Acids for use in the reactions include organic acids, e.g. carboxylic acids such as acetic acid.

The reactions may be performed at any suitable temperature, for example from around -78°C to ambient temperature or to the reflux temperature depending on the nature of the starting materials.

In general, the base, acid, solvent and reaction conditions may be selected depending on the nature of the starting materials, from a range of known alternatives for reactions of this type.

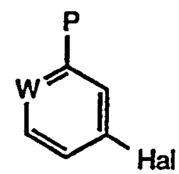
In silane derivatives of formula $(Alk^a)_3SiCH(R^5)(R^6)$, Alk^a may be for example a C_{1-6}alkyl group such as a methyl group. Derivatives of this type may be prepared for example by reacting a compound R^5-CH_2-R^6 with a silane derivative, such as a chlorotrialkylsilane, e.g. chlorotrimethylsilane in the presence of a base, e.g. lithium diisopropylamide, in a solvent, e.g. tetrahydrofuran, at a low temperature, e.g. around -10°C.

The starting materials R^5COR^6 and $R^5CH_2R^6$ are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds.

Intermediates of formula (9) where -W^a is a -C(O)R^4 group where R^4 is an alkyl or aryl group $(CH_2)_t$Ar group, may be prepared by reacting an aldehyde of formula (9) where -W^a is a -CHO group with an organometallic reagent in a solvent, e.g. tetrahydrofuran, at low temperature, e.g. around 10°C, followed by oxidation with an oxidising agent, such as manganese dioxide, in a solvent, e.g. dichloromethane.

Intermediates of formula (9) where $-W^a$ is -CHO may be prepared by reacting a compound of formula (8) described above with an organometallic reagent, such as n-butyllithium, in a solvent, such as an amide, e.g. dimethylformamide, at a low temperature, e.g. below -60°C.

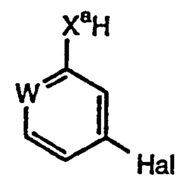
Intermediates of formula (8) may be prepared by deprotecting a compound of formula (10)



(10)

using reagents and conditions described herein for the obtention of an intermediate of formula (3) from an intermediate of formula (4) where L^2 is a group X^aH.

Intermediates of formula (10) may be prepared by protecting a compound of formula (11)



(11)

Examples of protecting groups include hydroxy, thio or amino protecting groups using conventional procedures [see Green, T. W. ibid]. Thus for example, where X^a is an oxygen atom, the hydroxyl group may be protected as an ether group, using a reagent Alk^bL^3, where Alk^b is an alkyl group and L^3 is a leaving group. Alkyl groups represented by Alk^b include cycloalkyl groups, such as cyclopentyl group, and leaving groups L^3 include halogen atoms such as iodine, chlorine or bromine atoms or sulphonyloxy groups such as arylsulphonyloxy groups, e.g. p.toluenesulphonyloxy groups.

The reaction may be carried out in the presence of a base, e.g. an inorganic base such as a carbonate, e.g. caesium or potassium carbonate,

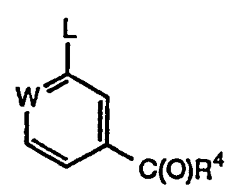
an alkoxide, e.g. potassium-t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran, at ambient temperature or above. e.g. around 40°C to 50°C.

Halides of formula (11) where X^a is -O- may be prepared by oxydation of an aldehyde of formula (17) (where R is a hydrogen atom) as described below using an oxidising agent such as 3-chloroperoxybenzoic acid in a halogenated hydrocarbon such as chloroform at a temperature from around 0°C to room temperature.

Halides of formula (11) where X^a is -S- or -N(R^b)- are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds.

Compounds of formula (1) where Z is a group (A) in which R^3 is a hydroxyl group and R^7 is as described for compounds of formula (1) may be prepared by reacting a compound or formula (11) with a reagent R^5R^6CHM or $R^5CHR^6R^7$ using the conditions described hereinabove for the obtention of an intermediate of formula (3) from a ketone of formula (5).

In another process according to the invention, compounds of formula (1) where Z is a group (B) and R^4 is a hydrogen atom or an alkyl or $-(CH_2)_tAr$ group may be prepared by reacting a compound of formula (12)



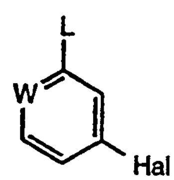
(12)

with a phosphonate ester $(R^dO)(OR^e)P(O)CH(R^5)(R^6)$ [where R^d and R^e, which may be the same or different is an alkyl, or aralkyl group] in the presence of a base in a suitable solvent.

Suitable bases include organometallic bases such as organolithium, e.g. n-butyllithium, alkoxides, for example alkali metal alkoxides such as sodium ethoxide or sodium methoxide and a hydride such as potassium hydride or sodium hydride. Solvents include ethers, e.g. diethylether or cyclic ethers such as tetrahydrofuran and alcohol, e.g. methanol or ethanol.

The phosphonate derivatives used in this reaction are either known compounds or may be prepared by reacting a phosphite $P(OR^d)_2(OR^e)$ with a compound R^5CHR^6Hal [where Hal is a halogen atom, for example a bromine atom] using conventional methods.

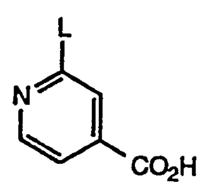
Intermediates of formula (12) where R^4 is a hydrogen atom may be prepared by reacting a halide of formula (13)



(13)

where Hal is a halogen atom, e.g. a bromine or chlorine atom with an organometallic reagent using the same reagents and conditions described above for the preparation of intermediates of formula (9) where W^a is -CHO from intermediates of formula (8).

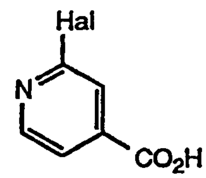
Intermediates of formula (2) where =W- is =N- and R^4 is H may be prepared from an acid of formula (14)



(14)

using the conditions described above for the preparation of an intermediate of formula (5) from an acid of formula (6).

Intermediates of formula (14) where L is $X^aAlk'Ar'$ or X^aR' and $-X^a$ is -O-, -S- or -NH-, may be prepared by reacting a halide of formula (15)

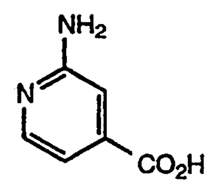


(15)

where Hal is a halogen atom, e.g. a bromine, chlorine or iodine atom with a compound $ArAlk'X^aH$, where $-X^a$ is -O-, -S- or -NH- in the presence of a base.

Bases used in this reaction include a hydride, such as sodium hydride, or an organometallic base such as butyllithium in a solvent, such as an amide, for example dimethylformamide at a temperature from room temperature to above, e.g. 80°C.

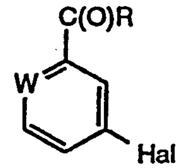
Intermediates of formula (15) may be prepared by reacting the known amine of formula (16)



(16)

with nitrous acid (made *in situ* by reacting sodium nitrite with an acid, for example sulphuric acid or hydrobromic acid) to produce the diazonium salt. This in turn may be reacted with a haloacid, e.g. hydrobromic, hydrochloride or hydriodic acid if necessary in the presence of the corresponding copper (I), halide (CuBr or CuI) or halogen Br_2, Cl_2 or I_2.

Intermediates of formula (13) where L is a $-C(R)=C(R^1)(R^2)$ group may be prepared by coupling a compound of formula (17)

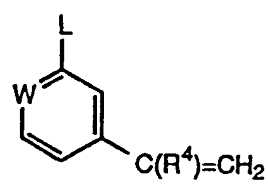


(17)

where Hal is a halogen atom, e.g. a bromine atom with a phosphonium salt $(R^1)(R^2)CHP(D)_3Hal$ as described below for the preparation of compounds of formula (1) from intermediates of formula (19).

Intermediates of formula (12) where R^4 is an alkyl or $-(CH_2)_tAr$ group may be prepared by reaction of the corresponding compound of formula (12) where R^4 is a hydrogen atom with an organometallic reagent, followed by oxidation, as described previously for the preparation of intermediates of formula (9) where W^a is $-C(O)R^4$ where R^4 is an alkyl or aryl group $(CH_2)_tAr$ from intermediates of formula (9) where R^4 is a hydrogen atom.

In another process for the preparation of compounds of formula (1) where Z is the group (B), an intermediate of formula (18)

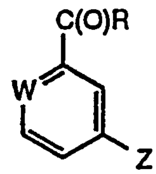


(18)

may be coupled in a Heck reaction with an organopalladium compound derived from a compound R^5Hal [where Hal is a halogen atom such as a bromine atom] and a palladium salt such as palladium acetate in the presence of a phosphine such as tri-o-tolylphosphine and a base such as triethylamine at an elevated temperature and pressure.

Intermediate alkenes of formula (18) may be obtained by reaction of a corresponding intermediate of formula (12) using a Wittig reaction employing a phosphonium salt such as methyltriphenylphosphonium bromide in the presence of a base such as n-butyllithium and an inert solvent such as tetrahydrofuran at, for example, 0°C to ambient temperature.

Intermediates of formula (3) where L^2 is a -Alk'L^3 group in which Alk' is an alkenylene chain -C=C-Alk'- and L^3 is a hydroxyl group may be prepared by coupling a compound of formula (19)



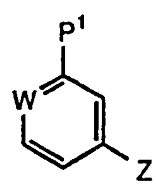
(19)

where R is a hydrogen atom or an alkyl group such as a methyl group, with an olefination agent.

Particular examples of olefination agents include phosphonium salts such as compounds HOAlk'P(D)$_3$Hal [where the hydroxyl group may need to be protected using conventional protecting group] where Hal is a halogen atom, such as a bromine atom and D is an optionally substituted alkyl, e.g. methyl, or aryl, especially phenyl group; phosphoranes HOAlk'C=P(D)$_3$; phosphonates (DO)$_2$P(O)Alk'OH; or silane derivatives, for example compounds of formula (D)$_3$SiAlk'OH e.g. trialkylsilanes such as $(CH_3)_3$SiAlk'OH.

Intermediates of formula (19) where R is an alkyl group, may be prepared by reacting an intermediate of formula (19) where R is a hydrogen atom with an organometallic reagent, such as an alkyllithium or an organomagnesium RMgHal, using the conditions described above, followed by oxidation of the resulting alcohol, using an oxidising agent, e.g. manganese dioxide.

Intermediates of formula (19) where R is a hydrogen atom may be prepared by deprotecting a protected aldehyde of formula (20)



(20)

where P^1 is a protected aldehyde group, e.g. a dioxanyl group, using acid hydrolysis e.g. by reaction with trifluoroacetic acid or p-toluene sulphonic acid, in the presence of a solvent, e.g. acetone, or a mixture of solvents, e.g. chloroform and water.

Intermediates of formula (20) may be prepared by protecting an aldehyde or ketone of formula (19) with an aldehyde or ketone protecting group, using for example a suitable diol, e.g. 1,3-propanediol, in the presence of an acid catalyst, e.g. 4-toluene sulphonic acid, in a solvent, such as an aromatic solvent, e.g. toluene, at an elevated temperature.

In general, this reaction may be used when it is desired to protect an aldehyde in any intermediate described herein.

Compounds of formula (1) where L is a group $-C(R)=C(R^1)(R^2)$ or Alk'Ar' where Alk' is an alkenylene chain -C=C-Alk' may be prepared from an intermediate of formula (19) using an appropriate olefination agent.

Particular examples of olefination agents include phosphonium salts such as compounds $(R^1)(R^2)CHP(D)_3Hal$ or $Ar'Alk'P(D)_3Hal$ where Hal is a halogen atom, such as a bromine atom, and D is an optionally substituted alkyl, e.g. methyl, or aryl, especially phenyl, group; phosphoranes $(R^1)(R^2)C=P(D)_3$ or $Ar'Alk'=P(D)_3$; phosphonates $(DO)_2P(O)CH(R^1)(R^2)$ or $(DO_2)P(O)Alk'Ar'$; or silane derivatives, for example compounds of formula $(D_3)SiC(R^1)(R^2)$ or $(D_3)SiAlk'Ar'$, e.g. trialkylsilanes such as $(CH_3)_3SiC(R^1)(R^2)$ or $(CH_3)_3SiAlk'Ar'$,

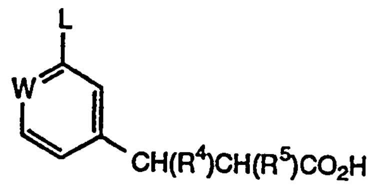
triamide; a non-polar solvent, such as an ether, e.g. tetrahydrofuran or diethyl ether or an aromatic solvent such as benzene, toluene or xylene; or a polar protic solvent, such as an alcohol, for example ethanol. Preferably the reaction is carried out at a low temperature, for example from around -78°C to around room temperature.

The olefination agents used in this reaction are either known compounds or may be prepared from known starting materials using reagents and conditions similar to those used to prepare the known compounds. For example, a phosphorane may be prepared in situ by reaction of a phosphonium salt with a base of the type described above. In another example, a phosphonate reagent may be prepared by reacting a halide Alk'Hal with a phosphite $(DO)_3P$, as described in the Arbuzov reaction. Silane derivatives may be prepared by reaction of a halosilane $(D)_3SiHal$ where Hal is a halogen atom, for example a chlorine atom, with a base, such as lithium diisopropylamide, in a solvent, such as an ether, for example a cyclic ether, e.g. tetrahydrofuran, at low temperature, e.g. -10°C.

According to a further aspect of the invention, compounds of formula (1) where L is a group $-C(R)=CH(R^1)$ and R^1 is an optionally substituted alkyl, alkenyl or alkenyl group may also be prepared by reaction of an intermediate of formula (19) with an organometallic reagent, followed by dehydration of the corresponding alcohol.

Examples of organometallic reagents include organolithium R^1Li or organomagnesium R^1MgHal reagents. The reaction with the organometallic reagent may be performed in a solvent such as an ether, e.g. diethyl ether or for example a cyclic ether such as tetrahydrofuran, at a low temperature for example -10°C to room temperature. The dehydration may be performed using an acid, for example an organic acid such as p.toluene sulphonic acid or trifluoracetic acid, in the presence of a base, such as an amine, e.g. triethylamine.

In yet another process according to the invention, compounds of formula (1) wherein R^3, R^6 and R^7 is each a hydrogen atom may be prepared by decarboxylation of an acid of formula (21):

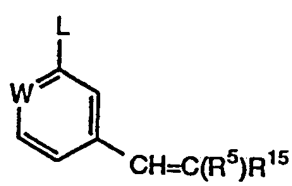


(21)

The reaction may be carried out by treatment of the compound of formula (21) with a base, for example an inorganic base such as a hydroxide, e.g. sodium hydroxide in a solvent such as an alcohol, e.g. ethanol, at an elevated temperature e.g. the reflux temperature, followed by acidification of the reaction mixture to a pH of around pH4 to around pH6 using an acid such as an inorganic acid, e.g. hydrochloric acid, at an elevated temperature, e.g. the reflux temperature.

If desired, the acid of formula (21) may be generated *in situ* from the corresponding ester or nitrile using the above reaction conditions, or by initial treatment with an acid.

Intermediates of formula (21) may be prepared by reacting a compound of formula (22)



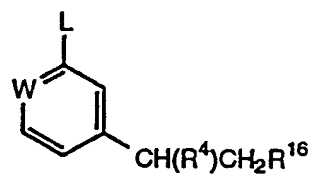
(22)

[where R^{15} is an ester of an acid $-CO_2H$ (e.g. an alkyl ester such as an ethyl ester) or a nitrile -CN], with a Grignard reagent R^4MgBr, in the presence of a complexing agent, e.g. a copper (I) bromide-dimethyl sulphide complex, or a copper (I) chloride, or with an organolithium compound, e.g. R^4Li, in a solvent, e.g. tetrahydrofuran, at low temperature, e.g. around -40°C, followed by treatment with a base or an acid to yield the acid of formula (21). The Grignard and the lithium

reagents are either known compounds or may be prepared in a manner similar to that used to synthesise the known compounds.

Compounds of formula (22) may be obtained by reacting an adehyde of formula (12) with an ester or nitrile $R^5CH_2R^{15}$ in an acid solvent, such as acetic acid, at an elevated temperature, for example the reflux temperature, in the presence of a base, such as ammonium acetate.

In a further process according to the invention a compound of formula (1) wherein R^3, R^6 and R^7 is each a hydrogen atom and R^5 is a heteroaryl group may be generally prepared by cyclisation of a compound of formula (23):



(23)

where R^{16} is a carboxylic acid [$-CO_2H$] group or a reactive derivative thereof; or a nitrile [-CN] or an imine salt with a bifunctional reagent $W^1R^{5a}W^2$ and, where necessary, a compound $R^{5b}W^3$ [where W^1, W^2 and W^3, which may be the same or different, is each a reactive functional group or a protected derivative thereof; and R^{5a} and R^{5b} are components of the heteroaryl group R^5 such that when added together with W^1, W^2 and W^3 to the group R^{16} in compounds of formula (23) the resulting group $-RW^1R^{5a}W^2$ or $-RW^1R^{5a}W^2R^{5b}W^3$ constitutes the heteroaryl group R^5].

Reactive derivatives of carboxylic acids for use in this reaction include acid halides, (e.g. acid chlorides), amides, including thioamides, or esters, including thioesters. Imine salts include for example salts of formula [e.g.-$C(OAlk)=NH_2^+A^-$, where Alk is a C_{1-4}alkyl group and A^- is a counterion e.g. a chloride ion].

In this general reaction the reactive functional groups represented by W^1, W^2 or W^3 may be any suitable carbon, nitrogen, sulphur or oxygen nucleophiles. Particular examples include simple nucleophiles such as

carbanions [e.g. generated by the coupling of an alkyl group with an organometallic compound], amino, thiol and hydroxyl groups.

In general, the cyclisation reaction will initially be performed in a solvent, for example an inert solvent such as a halocarbon, e.g. dichloromethane, an ether, e.g. a cyclic ether such as tetrahydrofuran, or a hydrocarbon, e.g. an aromatic hydrocarbon such as toluene, from a low temperature, e.g. around -70°C, to around the reflux temperature, where necessary in the presence of a base or a thiation reagent, e.g. Lawesson's reagent, followed if necessary by heating, to an elevated temperature, e.g. the reflux temperature.

Thus, in one particular example, compounds of formula (1) wherein R^3, R^6 and R^7 is each a hydrogen atom and R^5 is a benzothiazolyl, benzoxazolyl or benzimidazolyl group may be prepared by reaction of a compound of formula (19) where R^{16} is an acid halide, e.g. acid chloride, with a reagent $W^1R^{5a}W^2$ which is 2-aminothiophenol, 2-hydroxyphenol, or 1,2-diaminobenzene respectively in the presence of a base e.g. an organic amine such as pyridine, in a solvent e.g. a halocarbon such as dichloromethane, from around -70°C to the reflux temperature.

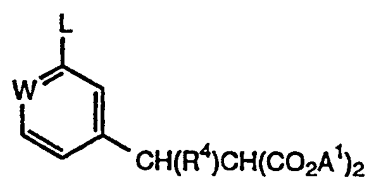
In another example of the general cyclisation process, a compound of formula (23) where R^{16} is an acid halide as described above may be reacted with a compound $W^1R^{5a}W^2$ which is a monoalkylmalonate, e.g. ethyl hydrogen malonate, followed by reaction with a compound $R^{5b}W^3$ which is hydrazine to give a compound of formula (1) wherein R^3, R^6 and R^7 is each a hydrogen atom and R^5 is a 5-hydroxypyrazolyl group.

In another variation of the cyclisation process, the halide of formula (23) may be reacted with a compound $W^1R^{5a}W^2$ which is $BrMg(CH_2)_3[-O(CH_2)_2O-]$ followed by reaction in an acid solution with a compound $R^{5b}W^3$ which is methylamine to yield a compound of formula (1) wherein R^3, R^6 and R^7 is each a hydrogen atom and R^5 is a N-methyl pyrrole group.

In a further example of the cyclisation process, the acid halide of formula (23) may be reacted with a compound $W^1R^{5a}W^2$ which is $H_2NNHCSNH_2$ in an aromatic hydrocarbon such as toluene, at an elevated temperature, e.g. around 150°C, followed by treatment with a base, e.g. an inorganic base such as sodium bicarbonate to give a compound of formula (1) wherein R^3, R^6 and R^7 is each a hydrogen atom and R^5 is a 1,2,4-triazolyl-5-thiolate group.

Intermediate compounds of formula (23) are particularly useful and form a further aspect of the invention. Active derivatives of the acids of formula (23) and other compounds of formula (23) where R^{16} is a nitrile or an imine salt may be prepared from the corresponding acids [where R^{16} is $-CO_2H$] using conventional procedures for converting carboxylic acids to such compounds, for example as described in the Examples hereinafter.

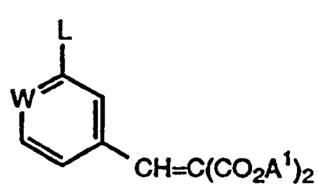
Acids of formula (23) [where R^{16} is $-CO_2H$] may be prepared by hydrolysing a diester of formula (24)



(24)

where A^1 is a C_{1-4}alkyl group, e.g. an ethyl group, with a base, e.g. sodium hydroxide, in a solvent, e.g. dioxane, at an elevated temperature, e.g. the reflux temperature, followed by acidification at an elevated temperature.

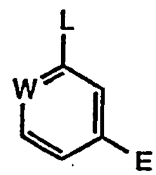
Diesters of formula (24) may be prepared by reacting a diester of formula (24)



(24)

with an organometallic reagent, such as a Grignard reagent using the conditions described above for the preparation of alcohols of formula (1).

In yet another process according to the invention, a compound of formula (1) where Z is a group (C) may be prepared by coupling a compound of formula (25),


(25)

where E is a boronic acid $-B(OH)_2$ or a tin reagent $Sn(R)_3$, in which R is an alkyl group, for example a methyl group, with a reagent $Z\text{-}L^4$, where L^4 is a leaving group, in the presence of a complex metal catalyst.

Particular leaving groups L^4 include for example halogen atoms, e.g. bromine, iodine or chlorine atoms and an alkyl sulphonate, such as trifluoromethanesulphonate.

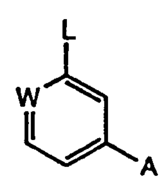
Suitable catalysts include heavy metal catalysts, for example palladium catalysts, such as tetrakis (triphenylphosphine)palladium. The reaction may be performed in an inert solvent, for example an aromatic hydrocarbon such as toluene or benzene, or an ether, such as dimethoxyethane or dioxane, if necessary in the presence of a base, e.g. an alkali carbonate such as sodium carbonate, at an elevated temperature, e.g. the reflux temperature. In general, the metal catalyst and reaction conditions may be selected, depending on the nature of the compound of formula (25) and/or the compound $Z\text{-}L^4$ from a range of known alternatives for reactions of this type [see for example Miyaura, N *et al*, Synth. Comm. (1981), 11, 513; Thompson, W. J. and Gaudino, J., J. Org. Chem, (1984), 49, 5237 and Sharp, M. J. *et al*, Tetrahedron Lett. (1987), 28, 5093].

Intermediates $Z\text{-}L^4$ are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds. Thus, for example, where it is desired to obtain a compound $Z\text{-}L^4$ where L^4 is a halogen atom such as bromine or chlorine atom and this compound is not readily available, such

a compound may be prepared by (1) treatment of the corresponding amine with t-butyl nitrite and anhydrous $CuCl_2$ or $CuBr_2$ at elevated temperature, or (2) with t-butyl thionitrite or t-butyl thionitrate and $CuCl_2$ or $CuBr_2$ at room temperature followed by reaction with an appropriate copper (I) halide such as cuprous chloride or bromide in an aqueous acid.

Intermediates of formula (25) may be prepared by halogen-metal exchange between a compound of formula (13) where Hal is a bromine atom and an organometallic agent such as n-butyl or t-butyllithium followed by reaction with a borate such as triisopropylborate or a tin reagent $(R)_3SnX$, where R is as described above and X is a halogen atom, such as chlorine atom, optionally at a low temperature e.g. around -70°C, in a solvent such as tetrahydrofuran.

According to another aspect of the invention, a compound of formula (1) where Z is a group (D) in which $-Z^1$ is $-NR^{12}C(O)-$ or $-C(O)NR^{12}-$ may be prepared by coupling a compound of formula (26)



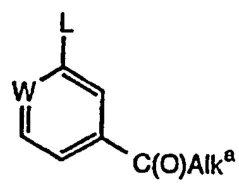
(26)

where -A is a $-CO_2H$ or $-NHR^{12}$ group,
or an active derivative thereof with a compound $R^{12}NH(Alk)_t(X)_nAr$ or $Ar(X)_n(Alk)_tCO_2H$ or an active derivative thereof. Active derivatives of acids of formula (26) or $Ar(X)_n(Alk)_tCO_2H$ include, for example, acid anhydrides, or acid halides, such as acid chlorides.

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example, the reaction may be carried out in a solvent, for example an inert organic solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, an amide, e.g. a substituted amide such as dimethylformamide, or a halogenated hydrocarbon such as dichloromethane, at a low temperature, e.g. -30°C to ambient temperature such as -20°C to 0°C, optionally in the presence of a base, e.g. an organic

base such as an amine, e.g. triethylamine or a cyclic amine such as N-methylmorpholine. Where an acid of formula (17) or $Ar(X)_n(Alk)_tCO_2H$ is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a triazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to reaction with the amine.

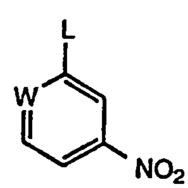
Intermediate acids of formula (26) where A is a $-CO_2H$ group may be prepared by hydrolysis of a corresponding ester of formula (27)



(27)

where Alk^a is an alkyl group;
by heating in the presence of a base, for example an alkali metal hydroxide such as lithium hydroxide in a solvent such as an alcohol, e.g. methanol.

Intermediates of formula (26) where A is a $-NHR^{12}$ group and R^{12} is a hydrogen atom, may be prepared by hydrogenation of a corresponding nitro compound of formula (28)



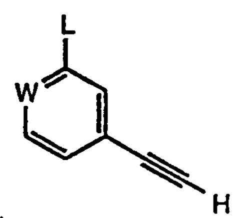
(28)

using the reagents described below for the hydrogenation of a compound of formula (1) where -L is a $-CH=C(R^1)(R^2)$ chain to a compound of formula (1) where -L is a $-CH_2CH(R^1)(R^2)$ chain.

Intermediates of formula (26) where A is a NHR^{12} group in which R^{12} is an alkyl group may be prepared by alkylation of an intermediate of formula (26) in which R^{12} is a hydrogen atom, using an alkyl halide e.g. an alkyl iodide in a solvent, such as an aromatic solvent, for example benzene.

Intermediates of formulae (27) and (28) and the reagents $R^{12}NH(Alk)_t(X)_nAr$ and $Ar(X)_n(Alk)_tCO_2H$ are known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds.

In yet another aspect of the invention compounds of formula (1) where Z is a group(D) in which Z^1 is a -C≡C- chain and n and t is each zero may be prepared by reacting a compound of formula (29)



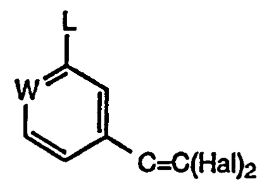
(29)

with a reagent $Ar(X)_n(Alk)_tL^5$ (where L^5 is a leaving group) in the presence of a metal complex catalyst, and in a solvent

Examples of L^5 leaving groups include halogen atoms such as bromine, iodine or chlorine atoms or alkyl triflate such as trifluoromethane sulphonate. Suitable solvents include for example an amine, for example a tertiary amine, e.g. triethylamine, a secondary amine, e.g. dimethylamine or a primary amine e.g. n-butylamine.

Metal complex catalysts include palladium catalysts, such as $Pd(Hal)_2(PPh_3)_2$ or $Pd(PPh_3)_4$ (where Hal is a halogen atom e.g. a chlorine atom) in the presence of copper (I) iodide, at a temperature from room temperature to an elevated temperature, e.g. the reflux temperature. (Comprehensive organic synthesis, vol. 3., 531-541; Trost, Fleming. Pergamon Press, 1991).

Intermediates of formula (29) may be prepared by reacting a dihalide of formula (30)

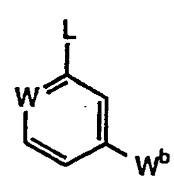


(30)

where Hal is a halogen atom, e.g. a bromine atom, with a base such as an organometallic base, for example an organolithium, e.g. n-butyllithium, in a solvent such as an ether, e.g. tetrahydrofuran or diethylether, at a temperature from around -78°C to room temperature.

Intermediates of formula (30) may be prepared by reacting an aldehyde of formula (12) (where R^4 is a hydrogen atom) with a reagent $Hal_2C{=}P(Ar^1)_3$ (where Hal is a halogen atom, such as a bromine atom and Ar^1 is an aryl group, such as phenyl or o-tolyl), prepared in situ from $C(Hal)_4$ and $P(Ar^1)_3$ in the presence of a base, such a an organometallic base, for example an organolithium, e.g. n-butyllithium).

In a futher aspect of the invention, compounds of formula (1) where Z is a group (D) in which Z^1 is a $-NR^{12}SO_2-$ or $-SO_2NR^{12}-$ group may be prepared by reaction of a compound of formula (30)



(30)

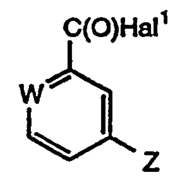
where (a) W^b is a $-NHR^{12}$ group with a compound $Ar(X)_n(Alk)_tSO_2Hal$ [where Hal is a halogen atom, e.g. a bromine or chlorine atom], if necessary in the presence of a base; or,
(b) W^b is a $-SO_2Hal$ group with a compound $Ar(X)_n(Alk)_tNHR^{12}$ using the reagents and conditions described in (a) above.

Examples of bases used in this reaction include amine, such as tertiary amine, for example triethylamine, in a solvent such as an ether, for example a cyclic ether, e.g. tetrahydrofuran.

Compounds Ar $(X)_n(Alk)_tNHR^{12}$ and compounds of formula (30) where W^b is a $-NHR^{12}$ group are known compounds or may be prepared using similar reagents and conditions to those used to prepare the known compounds.

Compounds of formula (30) where W^b is $-SO_2Hal$, may be prepared by reacting an intermediate halide of formula (13) with an organometallic reagent, such as an organolithium, e.g. n-butyllithium in a solvent, such as an ether, e.g. tetrahydrofuran, at a low temperature e.g. around -60°C to -100°C followed by reaction with sulphuryl chloride, in a solvent, such as an aliphatic solvent, e.g. n-hexane, at a low temperature, e.g. around 0°C.

Compounds of formula (1) where L is a group $-CH(R^1)(R^2)$ where R^2 is a $-CO_2H$ group may be prepared by reacting a compound of formula (31)



(31)

where Hal^1 is a halogen atom, such as a chlorine or a bromine atom, with a diazoalkane $CH(R^1)N_2$ to give the corresponding diazoketone derivative which is then treated with water and silver oxide or with silver benzoate and triethylamine.

Intermediates of formula (31) may be prepared by oxidation of an aldehyde of formula (19), using an oxidising agent, such as permanganate or chromic acid, to give the corresponding carboxylic acid which is then reacted with a halide reagent, such as thionylchloride, phosphorous pentachloride or phosphorous pentabromide.

Compounds of formula (1) may also be prepared by interconverting other compounds of formula (1). Thus, for example where Z is a group (A) in

which R^3 is a hydrogen atom may be prepared by hydrogenation of a compound of formula (1) where Z is a group (B).

The hydrogenation may be performed using for example hydrogen in the presence of a catalyst. Suitable catalysts include metals such as platinum or palladium optionally supported on an inert carrier such as carbon or calcium carbonate; nickel, e.g. Raney nickel, or rhodium. The reaction may be performed in a suitable solvent, for example an alcohol such as methanol or ethanol, an ether such as tetrahydrofuran or dioxane, or an ester such as ethyl acetate, optionally in the presence of a base, for example a tertiary organic base such as triethylamine, at for example ambient temperature.

Alternatively, the reaction may be accomplished by transfer hydrogenation using an organic hydrogen donor and a transfer agent. Suitable hydrogen donors include for example acids, such as formic acid, formates, e.g. ammonium formate, alcohols, such as benzyl alcohol or ethylene glycol, hydrazine, and cycloalkenes such as cyclohexene or cyclohexadiene. The transfer agent may be for example a transition metal, for example palladium or platinum, optionally supported on an inert carrier as discussed above, nickel, e.g. Raney nickel, ruthenium, e.g. tris (triphenylphosphine) ruthenium chloride or copper. The reaction may generally be performed at an ambient or elevated temperature, optionally in the presence of a solvent, for example an alcohol such as ethanol or an acid such as acetic acid.

In a second example of an interconversion process, compounds of formula (1) where Z is a group (A) in which R^7 is an OR^c group where R^c is an alkyl or alkenyl group, may be prepared by reacting a compound of formula (1) where Z is a group (A) in which R^7 is a -OH group, with a reagent R^c-OH, in the presence of an acid, such as sulphuric acid.

In another example of an interconversion process, compounds of formula (1) where Z is a group (A) in which R^7 is an OR^c group where R^c is a carboxamido or thiocarboxamido group may be prepared by reaction of a compound of formula (1) where Z is a group (A) in which R^7 is a -OH

group, with an isocyanate $R^cN{=}C{=}O$ or an isothiocyanate $R^cN{=}C{=}S$ in the presence of a base, such as sodium hydride, in a solvent, such as tetrahydrofuran. Compounds $R^cN{=}C{=}O$ and $R^cN{=}C{=}S$ are known compounds or may be prepared using the reagents and conditions used for the preparation of the known compounds. When $R^cN{=}C{=}S$ is not available, a compound of formula (1) where R^c is a thiocarboxamido group may be prepared by interconverting a compound of formula (1) where R^c is a carboxamido group using a thiation reagent, such as Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulphide], in an aromatic solvent, such as xylene or toluene.

In a yet another example of an interconversion process, a compound of formula (1) where Z is a group (A) in which R^3 is a fluorine atom may be prepared by reacting a compound of formula (1) where Z is a group (A) in which R^3 is a hydroxyl group, with a fluorinating reagent, such as diethylaminosulphur trifluoride (DAST), in a solvent, for example a chlorinated solvent, e.g. dichloromethane, at a low temperature, e.g. around 0°C.

In a still further example of an interconversion process, a compound of formula (1) where Z is a group (A) in which R^3 is an alkyl group, may be prepared by alkylation of a compound of formula (1) where Z is a group (A), and R^3 is a hydrogen atom, with a reagent R^3L^3 using a base, for example n-butyllithium or lithium diisopropylamide. In this process, R^4 in the starting material is preferably an electron withdrawing group.

In a still further example of interconversion process, a compound of formula (1) where L is $(X^a)_n$Alk'Ar' or Alk'X^aAr' where Alk' is an alkylene chain, may be prepared by hydrogenation of a compound of formula (1) where Alk' is an alkenylene or alkynylene chain, using for example hydrogen in the presence of a metal catalyst, as described above for the hydrogenation of a compound of formula (1) where Z is a group (B) to give a compound of formula (1) where Z is the group A.

Compounds of formula (1) where Z is the group (B) may also be prepared by dehydrating a compound of formula (1) where Z is the group (A) and R^3

is a hydroxyl group, by using an acid, e.g. trifluoroacetic acid, in the presence of a base, such as an amine, e.g. triethylamine, in a solvent, such as dichloromethane, at a low temperature, e.g. around -10°C.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral acid or base. Suitable chiral acids include, for example, tartaric acid and other tartrates such as dibenzoyl tartrates and ditoluoyl tartrates, sulphonates such as camphor sulphonates, mandelic acid and other mandelates and phosphates such as 1,1'-binaphthalene-2,2'-diyl hydrogen phosphate. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid or base in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate acid or base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

The following Examples illustrate the invention. In the Examples, the following abbreviations are usedDME - ethylene glycol dimethyl ether; THF - tetrahydrofuran; CH_2Cl_2 - dichloromethane; Et_2O - ether; EtOH - ethanol; RT - room temperature; DMF - N, N-dimethylformamide; EtOAc - ethyl acetate; MeOH - methanol.

Intermediates 1-6 were prepared as described in International Patent Specification No. WO 94/14742.

INTERMEDIATE 1
3-Cyclopentyloxy-4-methoxybenzaldehyde

INTERMEDIATE 2
(3-Cyclopentyloxy-4-methoxyphenyl)phenylketone

INTERMEDIATE 3
(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxy-2-phenyl-ethyl] pyridine

INTERMEDIATE 4
(E) and (Z) isomers of 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethenyl] pyridine

INTERMEDIATE 5
(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl] pyridine

INTERMEDIATE 6
(i) (+) -4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl] pyridine
(ii) (-) -4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl] pyridine

INTERMEDIATE 7
a) (R) -4-[2-(3-Hydroxy-4-methoxyphenyl)-2-phenylethyl]pyridine
Intermediate 6 (i) (430mg) in dioxane/water (20ml:10ml) containing concentrated H_2SO_4 (10ml) was heated at 90°C for 1h. The reaction

mixture was cooled, neutralised with aqueous $NaHCO_3$ then concentrated *in vacuo*. The residue was partitioned between EtOAc (25ml) and H_2O (15ml), and the organic phase separated. The extract was washed with brine (25ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised (EtOH) to afford the title compound (240mg) as an off-white crystalline solid m.p. 195-197°C (Found: C, 78.66; H, 627; N, 4.59. $C_{20}H_{19}NO_2$ requires C, 78.64; H, 6.18; N, 4.42%); δ_H ($CDCl_3$) 3.30 (2H, d, J 8 Hz, $CHC\underline{H}_2$), 3.86 (3H, s, O$\underline{Me}$), 4.13 (1H, t, J 8Hz, $C\underline{H}CH_2$), 5.7 (1H, br s, O$\underline{H}$), 6.63 (1H, dd, J 8.3Hz, Ar$\underline{H}$ para to OH), 6.71 (1H, d, J 8.3Hz, Ar$\underline{H}$ ortho to OMe), 6.80 (1H, d, J 2.2Hz, Ar$\underline{H}$ ortho to OH), 6.93 (2H, dd, J 4.5, 1.5Hz, pyridine $\underline{H}_3$, $\underline{H}_5$), 7.1-7.3 (5H, m, C_6H_5), and 8.37 (2H, dd, J 4.5 ,1.5Hz, pyridine $\underline{H}_2$,$\underline{H}_6$).

The following Intermediate was prepared in a manner similar to Intermediate 7a)

b) **(E)-4-[2-(3-Hydroxy-4-methoxyphenyl)ethenyl]pyridine**

From Intermediate 20 (8.0g, 27.1mmol) in toluene (200ml) and p-toluenesulphonic acid H_2O (10.3g, 54.2mmol) under a nitrogen atmosphere. Recrystallisation (EtOH) gave the title compound (3.8g) as an amorphous yellow solid. m.p. 196-199°C. (Found C, 73.73; H, 6.03; N, 6.06. $C_{14}H_{13}NO_2$ requires C, 73.99; H, 5.77; N, 6.16%). δ_H (300 MHz; $CDCl_3$) 3.92 (3H, s, $OC\underline{H}_3$), 6.22 (1H, br s, O$\underline{H}$), 6.86 (1H, d, H 8.3Hz, Ar$\underline{H}_4$), 6.86 (1H, d, J 16.2Hz, $\underline{H}$C=C (trans)), 7.01 (1H, dd, J 8.3, 2.1Hz, Ar$\underline{H}_6$), 7.17-7.26 (2H, m, Ar$\underline{H}_2$ and $\underline{H}$C=C), 7.34 (2H, dd, J 4.6, 1.6Hz, pyridine $\underline{H}_3$, $\underline{H}_5$), and 8.55 (2H, t, J 4.6, 1.4Hz, pyridine $\underline{H}_2$,$\underline{H}_6$).

INTERMEDIATE 8

2-Methoxy-4-(3-pyridyl)benzaldehyde

A mixture of 5-bromo-2-methoxybenzaldehyde (10.00g, 1.82mmol) and tetrakis (triphenylphosphine)palladium (O) (2.10g, 1.82mmol, 3.9 mol%) in DME (filtered through Al_2O_3) (50ml) was stirred at RT for 0.25h. Sodium carbonate (2M, 50ml, 0.10mol%) and diethyl (3-pyridyl)borane (6.817g, 46.36mmol) were added, the mixture heated to reflux for 5.5h then allowed to stand at RT overnight. The dark brown reaction mixture was partitioned between water (50ml) and Et_2O (100ml) and the organic layer separated and combined with two further Et_2O extracts (1 x 50ml, 1 x 25ml). The

organic phase was extracted with 2N hydrochloric acid (2 x 50ml) then the aqueous extract was basified with 3M NaOH and extracted with Et_2O (1 x 150ml, 2 x 50ml). The combined organic extract was washed with brine (50ml), dried (Na_2SO_4), concentrated *in vacuo* then submitted to column chromatography [SiO_2; Et_2O] to furnish the title compound (3.318g) as a pale yellow solid (Found: C, 73.40; H, 5.20; N, 6.44. $C_{13}H_{11}NO_2$ requires C, 73.23; H, 5.20; N, 6.57%.)

INTERMEDIATE 9

2-(5-Bromo-2-methoxyphenyl)-1,3-dioxane

A mixture of 5-bromo-2-methoxybenzaldehyde (52.3g, 243mmol), 1,3-propanediol (30ml, 31.6g, 415mmol), and 4-toluenesulphonic acid (0.3g) in toluene (350ml) was heated to reflux in a Dean-Stark apparatus for 20h. The mixture was cooled to RT, washed with saturated $NaHCO_3$ solution (100ml), then the organic layer was separated and combined with a CH_2Cl_2 solution (100ml). The extract was washed (brine; 50ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a brown oil (66.2g). The crude product was distilled to afford the title compound (58.2g) as a colourless viscous oil b.p. 115-120°C, 0.02mmHg δ_H (80MHz; $CDCl_3$) 1.2-1.5 (1H, br m, $CH_2C\underline{H}HCH_2$), 1.9-2.4 (1H, m, $CH_2CH\underline{H}CH_2$), 3.78 (3H, s, O$\underline{Me}$), 3.6-4.4 (4H, m, $C\underline{H_2}CH_2C\underline{H_2}$), 5.76 (1H, s, OC$\underline{H}$), 6.67 (1H, d, J 8.8 Hz, Ar$\underline{H}$ ortho to OMe), 7.33 (1H, dd, J 8.8, 2.3 Hz, Ar$\underline{H}$ para to acetal), and 7.68 (1H, d, J 2.3Hz, Ar$\underline{H}$ ortho to acetal); m/z (EI) 274 (44%), 273 (31), 272 (45), 271 (27), 216 (34), 215 (47), 214 (35), 213 (44), 193 (34), 135 (22), and 87 (100).

INTERMEDIATE 10

3-[2-(1,3-Dioxanyl)]-4-methoxybenzaldehyde

n-BuLi (1,6M solution in hexane) (125ml, 200mmol, 1.06 equiv.) was added dropwise to a solution of Intermediate 9 (51.65g, 189mmol) in THF (250ml) at below -65°C. After 3.5h, DMF (20ml, 258mmol, 1.37 equiv.) was added at below -60°C. The reaction mixture was allowed to warm to RT then poured into hydrochloric acid (0.05 M; 500ml) and immediately extracted with CH_2Cl_2 (500ml, 2 x 150ml). The extract was washed (brine; 200ml), dried (K_2CO_3), and concentrated *in vacuo* to give a pale yellow oil (44.0g). The crude product was triturated with warm hexane (250ml) to

afford the title compound (38.75g) as an off-white crystalline solid δ_H (80MHz; $CDCl_3$) 1.3-1.6 (1H, br m, $CH_2C\underline{H}HCH_2$), 1.8-2.5 (1H, m, $CH_2CH\underline{H}CH_2$), 3.89 (3H, s, O$\underline{Me}$), 3.7-4.4 (4H, m, $C\underline{H_2}CH_2C\underline{H_2}$), 5.82 (1H, s, OC$\underline{H}$), 6.93 (1H, d, J 8.4 Hz, Ar$\underline{H}$ ortho to OMe), 7.82 (1H, dd, J 8.4, 2.2 Hz, Ar$\underline{H}$ para to acetal), 8.12 (1H, d, J 2.2 Hz, Ar$\underline{H}$ ortho to acetal), and 9.84 (1H, s, C$\underline{H}$O).

INTERMEDIATE 11

3-[3-(1,3-Dioxan-2-yl)-4-methoxyphenyl]-2-(4-pyridyl)propenenitrile

A mixture of Intermediate 10 (15.0g, 67.5mmol) and 4-pyridylacetonitrile hydrochloride (10.75g, 69.5mmol) was stirred at RT in a mixture of EtOH (300ml) and NaOH solution (3M; 40ml, 150mmol). After 1h, the precipitate was collected by filtration, washed with EtOH (50ml), then Et_2O (25ml) and dried *in vacuo* to afford the title compound (15.85g) as a very pale yellow solid δ_H (80MHz; $CDCl_3$) 1.3-1.7 (1H, br m, $CH_2C\underline{H}HCH_2$), 2.0-2.4 (1H, m, $CH_2CH\underline{H}CH_2$), 3.90 (3H, s, O$\underline{Me}$), 3.8-4.4 (4H, m, $C\underline{H_2}CH_2C\underline{H_2}$), 5.83 (1H, s, OC$\underline{H}$), 6.95 (1H, d, J 8.5 Hz, Ar$\underline{H}$ ortho to OMe), 7.47 (2H, dd, J 4.6, 1.7 Hz, pyridine $\underline{H_3}$, $\underline{H_5}$), 7.63 (1H, s, C$\underline{H}$ = C), 7.96 (1H, d, J 2.4Hz, Ar$\underline{H}$ ortho to acetal), 8.20 (1H, dd, J 8.5, 2.4 Hz, Ar$\underline{H}$ para to acetal), and 8.61 (2H, dd, J 4.6, 1.7 Hz, pyridine $\underline{H_2}$, $\underline{H_6}$).

INTERMEDIATE 12

5-Bromo-2-methoxybenzylidenecyclopentane

n-BuLi (1.6M solution in hexane) (72.5ml, 116mmol) was added dropwise at 0°C to a solution of cyclopentyltriphenylphosphonium bromide (45.8g, 111mmol) in THF (300ml). The red solution was stirred at 0°C for 0.5h then treated with a solution of 5-bromo-2-methoxybenzaldehyde (23.5g, 109mmol) in THF (150 ml). The reaction mixture was stirred at RT overnight, concentrated *in vacuo*, then partitioned between CH_2Cl_2 (250ml) and water (150ml). The organic phase was separated and combined with further CH_2Cl_2 extracts (2 x 50ml). The organic phase was washed (brine; 50ml), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2; CH_2Cl_2) to afford the title compound (24.6g), as a colourless oil δ_H (80MHz; $CDCl_3$) 1.6-1.9 (4H, br m, $CH_2(C\underline{H_2})_2$), 2.3-2.6 (4H, br m, $C\underline{H_2}(CH_2)_2C\underline{H_2}$), 3.76 (3H, s, O$\underline{Me}$), 6.4-6.5 (1H, br m, C$\underline{H}$=C), 6.65 (1H, d, J 8.5Hz, Ar$\underline{H}$ ortho to OMe), 7.18

(1H, dd, J 8.5, 2.4Hz, ArH para to olefin), and 7.39 (1H, d, J 2.4 Hz, ArH ortho to olefin).

INTERMEDIATE 13

5-Formyl-2-methoxybenzylidenecyclopentane

n-BuLi (1.6M solution in hexane) (22ml, 27.7mmol, 1.1 equiv) was added dropwise at below -70°C to a solution of Intermediate 12 (6.81g, 25.5 mmol) in THF (50ml). The resulting orange solution was stirred for a further 0.5h then DMF (3.0ml, 39mmol, 1.5 equiv) was added at below -60°C. The reaction mixture was allowed to warm to RT, stirred for 1h, then treated with hydrochloric acid (10%; 100ml). After 1h, the mixture was extracted with CH_2Cl_2 (150ml, 2 x 50ml). The extract was washed (brine; 50ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a yellow oil (7.0g). The crude product was subjected to chromatography (SiO_2; Et_2O-hexane, 1:3) to afford the title compound (4.58g) as a colourless oil δ_H (80MHz; $CDCl_3$) 1.6-1.9 (4H, br m, $CH_2(C\underline{H_2})_2$), 2.4-2.65 (4H, br m, $C\underline{H_2}(CH_2)_2C\underline{H_2}$), 3.88 (3H, s, OMe), 6.45-6.6 (1H, br m, C<u>H</u>=C), 6.89 (1H, d, J 8.6Hz, ArH ortho to OMe), 7.59 (1H, d, J 2.2Hz, ArH ortho to olefin), 7.75 (1H, dd, J 8.6, 2.2Hz, ArH para to olefin), and 9.81 (1H, s, CHO).

INTERMEDIATE 14

2-[2-Methoxy-5-(phenylhydroxymethyl)]-1,3-dioxane

n-BuLi (1.6M solution in hexane) (115ml, 184mmol) was added dropwise at *ca* -70°C to a solution of Intermediate 9 (50.3g, 184mmol) in THF (1000ml). A solution of benzaldehyde (20.5g, 193mmol) in THF (100ml) was added dropwise at *ca* -70°C and the reaction mixture allowed to warm to RT over 3h. The mixture was quenched with 10% aqueous NH_4Cl solution (200ml) and the organic layer separated and combined with EtOAc extracts (3x100ml). The extract was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (61.0g) as a pale yellow crystalline solid. δ_H ($CDCl_3$) 1.47 (1H, br d, J ca 13Hz, $CH_2C\underline{H}CH_2$), 2.15-2.35 (2H, complex m, $CH_2C\underline{H}CH_2$+O<u>H</u>), 3.82 (3H, s, OMe), 3.99 (2H, ca. t, J ca. 11 Hz, $C\underline{H}CH_2C\underline{H}$), 4.23 (2H, dd, J ca. 11.4Hz, $C\underline{H}CH_2C\underline{H}$), 5.81 (1H, s, ArCH), 5.85 (1H, s, ArCH), 6.83 (1H, d, J 8.6Hz, ArH ortho to OMe), 7.2-7.4 (6H, m, $C_6\underline{H_5}$ + ArH para to dioxolane), and 7.68 (1H, d, J 2.3Hz, ArH ortho to dioxolane).

INTERMEDIATE 15

[3-(2-Dioxan-1,3-yl)-4-methoxy]benzophenone

A mixture of Intermediate 14 (60.0g, 200mmol) and manganese dioxide (174g, 2.0mol) in CH_2Cl_2 (1000ml) was stirred at RT for 18 h. The reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo*. The residue was recrystallised from diisopropyl ether-toluene to afford the title compound (41.0g) as a white solid. δ_H ($CDCl_3$) 1.41 (1H, br d, *J* 13.5Hz, $CH_2C\underline{H}CH_2$), 2.1-2.3 (1H, complex m, $CH_2C\underline{H}CH_2$), 3.93 (3H, s, O$\underline{Me}$), 3.99 (2H, dt, *J* 2.1, 12.3 Hz, $C\underline{H}CH_2C\underline{H}$), 4.23 (2H, dd, *J* 4.5,11.5Hz, $C\underline{H}CH_2C\underline{H}$), 5.87 (1H, s, ArC$\underline{H}$), 6.94 (1H, d, *J* 8.6Hz, Ar$\underline{H}$ ortho to OMe), 7.4-7.6 (3H, m, meta and para C_6H_5), 7.75 (2H, d, *J* 8.4Hz ortho C_6H_5), 7.84 (1H, dd, *J* 2.3, 8.6 Hz, Ar$\underline{H}$ para to dioxane), and 8.15 (1H, dd, *J* 2.3Hz, Ar$\underline{H}$ ortho to dioxane).

INTERMEDIATE 16

(±)-1-{3-[2-(1,3-Dioxanyl)]-4-methoxyphenyl}-1-phenyl-2-(4-pyridyl) ethanol

n-BuLi (2.5M solution in hexane) (55.6ml, 139mmol, 1.05equiv.) was added to a solution of 4-methylpyridine (11.9ml, 133mmol) in THF (500ml) at -70°C. The mixture was allowed to stir at -70°C for 0.5h then a solution of Intermediate 15 (40.0g, 133mmol) in THF (250ml) was added dropwise and allowed to warm to RT overnight. The reaction mixture was quenched with 10% aqueous NH_4Cl solution (100ml) and extracted with CH_2Cl_2 (300ml, 100ml). The extract was separated, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was recrystallised from EtOAc to afford the title compound (28.9g) as a white crystalline solid δ_H ($CDCl_3$) 1.41 (1H, br d, *J* 13.5Hz, $CH_2C\underline{H}CH_2$), 2.15-2.25 (1H, complex m, $CH_2C\underline{H}CH_2$), 2.4 (1H, br s, O$\underline{H}$), 3.54 (1H, d, *J* 13.1Hz, pyridine C$\underline{H}$),3.62 (1H, d, *J* 13.1Hz, pyridine C$\underline{H}$), 3.82 (3H, s, O$\underline{Me}$), 3.99 (2H, dt, *J* 2.1, 12.3 Hz, $C\underline{H}CH_2C\underline{H}$), 4.23 (2H, dd, *J* 5.1,10.7Hz, $C\underline{H}CH_2C\underline{H}$), 5.84 (1H, s, ArC$\underline{H}$), 6.75-6.85 (3H, m, Ar$\underline{H}$ meta/para to dioxane + C_6H_5 para $\underline{H}$), 7.15-7.35 (6H, m pyridine $\underline{H_3},\underline{H_5}$ + C_6H_5 ortho/meta $\underline{H}$), 7.76 (1H, d, *J* 2,3HZ, Ar$\underline{H}$ ortho to dioxane), and 8.30 (1H, dd, *J* 1.5, 4.5Hz, pyridine $\underline{H_2},\underline{H_6}$).

INTERMEDIATE 17

<u>(E, Z)-4-{2-[3-(2-Dioxan-1,3-yl)-4-methoxyphenyl]ethenyl}pyridine</u>

Trifluoroacetic anhydride (11.3ml, 80.2mmol) was added dropwise at <u>ca.</u> -10°C to a solution of Intermediate 16 (28.59g, 72.9 mmol) and triethylamine (15.2ml, 109.3mmol) in CH_2Cl_2 (500ml). The reaction mixture was stirred at -10°C for 0.5h then quenched with 10% aqueous sodium carbonate solution (250ml). The organic layer was separated and combined with further CH_2Cl_2 extracts (3x50ml), then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2; 5% MeOH CH_2Cl_2) to afford the <u>title compound</u> (20.0g) as a yellow solid. δ_H ($CDCl_3$) ('Hnmr indicates *ca* 3:1 mixture of isomers; data for major isomer, possibly <u>(E)</u>-, presented) 1.43 (1H, br d, <u>J</u> 12.6Hz, $CH_2C\underline{H}CH_2$), 2.15-2.35 (1H, complex m, $CH_2C\underline{H}CH_2$), 3.84 (3H, s, O<u>Me</u>), 4.01 (2H, <u>ca</u>. t, <u>J</u> 11.5 Hz, $C\underline{H}CH_2C\underline{H}$), 4.26 (2H, dd, <u>J</u> 4.9,11.5Hz, $C\underline{H}CH_2C\underline{H}$), 5.88 (1H, s, ArC<u>H</u>), 6.77 (1H, d, <u>J</u> 8.6 Hz, Ar<u>H</u> <u>ortho</u> to OMe), 6.81 (2H, d, <u>J</u> 5.8 Hz, pyridine $\underline{H}_3$, $\underline{H}_5$), 6.85 (1H, s, C=C<u>H</u>), 7.03 (1H, dd, <u>J</u> 2.3, 8.6 Hz, Ar<u>H</u> <u>para</u> to dioxane), 7.1-7.2 (2H, m, $C_6H_3\underline{H}_2$), 7.3-7.35 (3H, m, $C_6\underline{H}_3H_2$), 7.83 (1H, d, <u>J</u> 2.4 Hz, Ar<u>H</u> <u>ortho</u> to dioxane) and 8.30 (2H, d, <u>J</u> 5.8Hz, pyridine $\underline{H}_2$,$\underline{H}_6$).

<u>INTERMEDIATE 18</u>

<u>2-Methoxy-5-[1-phenyl-2-(4-pyridyl)ethyl]benzaldehyde</u>

A solution of Intermediate 17 (17.5g, 46.8mmol) in THF-MeOH (5:1; 1200ml) containing 10% Pd/C (0.5g) was hydrogenated at RT over 1h. The reaction mixture was filtered through Celite and then concentrated *in vacuo*. The crude alkane (15.0g) in THF (750ml) and 10% hydrochloric acid (75ml) was vigorously stirred at RT for 0.5h, then quenched with aqueous $NaHCO_3$ (2<u>M</u>; 100ml). The organic solvent was removed *in vacuo* and the aqueous phase extracted with EtOAC (3x100ml). The extract was dried ($MgSO_4$) and concentrated *in vacuo* to afford the <u>title compound</u> (12.6g). δ_H ($CDCl_3$) 3.34 (2H, d, <u>J</u> 8.0Hz, $CHC\underline{H}_2$pyridine), 3.87 (3H, s, O<u>Me</u>), 4.22 (1H, t, <u>J</u> 8.0Hz, $C\underline{H}CH_2$pyridine), 6.87 (1H, d, <u>J</u> 8.6 Hz, Ar<u>H</u> <u>ortho</u> to OMe), 6.92 (2H, d, <u>J</u> 6.0Hz, $\underline{H}_2$, $\underline{H}_6$ of C_6H_5), 7.1-7.3 (5H, m, pyridine $\underline{H}_3$, $\underline{H}_5$ + $\underline{H}_3$, $\underline{H}_4$, $\underline{H}_5$ of C_6H_5), 7.32 (1H, dd,<u>J</u> 2.4, 8.6Hz, Ar<u>H</u> <u>para</u> to CHO), 7.74 (1H, d, <u>J</u> 2.4Hz, Ar<u>H</u> <u>ortho</u> to CHO), 8.38 (2H, <u>ca</u>. d, <u>J</u> 4.5Hz, pyridine $\underline{H}_2$,$\underline{H}_6$) and 10.42 (1H, s, ArC<u>H</u>O).

INTERMEDIATE 19

(±)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxy thyl]pyridine

The title compound was prepared as described in the International Patent Application No. WO94/20446.

INTERMEDIATE 20

(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine

The title compound was prepared as described in the International Patent Application No. WO94/20446.

INTERMEDIATE 21

5-Phentylpentylbromide

To a stirred solution of 5-phenyl-1-pentanol (2.80g, 17.07mmol) in dry CH_2Cl_2 (80ml) at 0°C under a nitrogen atmosphere was added PBr_3 (4.62g, 1.62ml. 17.07mmol). The mixture was stirred at RT for 34min and quenched cautiously with saturated $NaHCO_3$ solution (100ml). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2x60ml). The combined organic extract was washed with water (80ml), dried ($MgSO_4$)and the residue subjected to chromatography (SiO_2) to give the title compound (0.69g) as a clear oil.

EXAMPLE 1

a) **(R)-4-[2-(3-Benzyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine**

Potassium *tert*-butoxide (180mg, 1.57mmol) was added to a stirred solution of Intermediate 7 (400mg, 1.31mmol) in THF (15ml) and DMF (5ml). The mixture was stirred at RT for 0.25h then treated with benzyl bromide (246mg, 1.44mmol). After 0.5h at RT, the reaction mixture was quenched with water (5ml) and concentrated *in vacuo*. The residue was partitioned between water (20ml) and EtOAc (30ml). The organic layer was separated and combined with further EtOAC extracts (2x30ml). The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give a pale brown oil which was subjected to chromatography (SiO_2; EtOAc-hexane, 17:3) to afford the title compound (434mg) as a colourless oil δ_H ($CDCl_3$) 3.18 (1H, dd, *J* 13.6, 8.4Hz, $CH\underline{H}_AH_B$), 3.25 (1H, dd, *J* 13.6, 7.4 Hz, $CHH_A\underline{H}_B$), 3.84 (3H, s, O$\underline{M}$e), 4.09 (1H, t, *J* 7.9Hz, $C\underline{H}CH_AH_B$), 5.08 (2H, s, OCH_2), 6.58-6.8 (3H, m, $C_6\underline{H}_3$), 6.82 (2H, dd, *J* 4.5, 1.6Hz, pyridine

$\underline{H}_3$, $\underline{H}_5$), 7.05-7.4 (10H, m, 2x$C_6\underline{H}_5$), and 8.35 (2H, dd, $\underline{J}$ 4.5,1.6Hz, pyridine $\underline{H}_2$,$\underline{H}_6$).

The following Example was prepared in a manner similar to compound of Example 1a).

b) **4-{2-(R)-[4-Methoxy-3-(phenylpentyloxy)phenyl]-2-phenylethyl} pyridine**

From Intermediate 7a) (0.29g, 0.95mmol) in THF (5ml) and DMF (3ml), potassium tert-butoxide (0.12g, 1.04mmol) and 5-phenylbromopentane (0.26g, 1.14mmol) in THF (5ml). Chromatography (SiO_2; EtOAc-hexane, 1:1) gave the title compound (0.33g) as a clear colourless oil. (Found C, 82.16; H, 7.38; N, 3.06. $C_{31}H_{33}NO_2$ requires C, 82.45; H, 7.37; N, 3.10%) δ_H (300MHz; $CDCl_3$) 1.40-1.85 (6H, m, $(C\underline{H}_2)_3$), 2.63 (2H, t, $\underline{J}$ 7.6Hz, $C_6H_5C\underline{H}_2$), 3.31 (2H, d, $\underline{J}$ 7.9Hz, $C\underline{H}_2$ pyridine), 3.81 (3H, s, $OC\underline{H}_3$), 3.90 (2H, dt, $\underline{J}$ 6.8, 1.6Hz, $OC\underline{H}_2$), 4.15 (1H, t, $\underline{J}$ 9Hz, $CH_2C\underline{H}$), 6.65 (1H, d, $\underline{J}$ 1.8Hz, $Ar\underline{H}_2$), 6.7-6.8 (2H, m, ArH), 6.92 (2H, dd, $\underline{J}$ 4.6, 1.4Hz, pyridine $\underline{H}_3$, $\underline{H}_5$), 7.15-7.30 (10H, m, 2x$C_6\underline{H}_5$), and 8.38 (2H ,dd, $\underline{J}$ 4.5, 1.5Hz, $\underline{H}_2$,$\underline{H}_6$ pyridine).

c) **(E)-4-[4-Methoxy-3-(5-phenylpentyloxy)phenylethenyl]pyridine**

From Intermediate 7b) (0.68g, 3.0mmol) potassium t-butoxide (0.40g, 3.6mmol) and Intermediate 21 (0.68g, 3.0mmol). Chromatography (SiO_2; EtOAc-hexane, 3:1) gave a slightly off-white solid (0.874g). A small portion (0.34g) was recrystallised (diisopropylether; 9ml) to give the title compound (0.312g) as an amorphous white solid (0.312g). m.p. 98-100°C. (Found C, 80.31; H, 7.27; N, 3.56. $C_{25}H_{27}NO_2$ requires C, 80.40; H, 7.29; N, 3.7%). δ_H (300MHz; $CDCl_3$) 1.5-2.0 (6H, m, $(C\underline{H}_2)_3$), 2.67 (2H. t. $\underline{J}$ 7.7Hz, $ArC\underline{H}_2$), 3.89 (3H, s, $OC\underline{H}_3$), 4.07 (2H, t, $\underline{J}$ 6.8 Hz, $OC\underline{H}_2$), 6.86 (1H, d, $\underline{J}$ 16.3, $\underline{H}C$=C), 6.88 (1H, d, $\underline{J}$ 8.9Hz, ArH), 7.07-7.31 (6H, m, ArH and $\underline{H}C$=C), 7.33 (2H, dd, $\underline{J}$ 4.6, 1.5Hz, pyridine $\underline{H}_3$, $\underline{H}_5$) and 8.55 (2H, dd, $\underline{J}$ 4.6, 1.5Hz pyridine $\underline{H}_2$,$\underline{H}_6$).

EXAMPLE 2

a) **(R)-4-[2-(4-Methoxy-3-(3-thienyloxy)phenyl)-2-phenylethyl] pyridine**

A mixture of Intermediate 7a) (500mg, 1.64mmol), anhydrous potassium carbonate (450mg, 3.28mmol) and 3-bromothiophene (3.48g, 21.3mmol) in pyridine (4ml) was heated to ca. 90°C. Copper (II) oxide (330mg, 4.1mmol) was added and the reaction mixture heated to reflux for 52h. CH_2Cl_2 (20ml) was added to the cooled reaction mixture which was then filtered. The filtrate was concentrated *in vacuo* and the residue subjected to chromatography (SiO_2; EtOAc-hexane, 17:3) to afford the title compound (315mg), as a colourless oil. (Found C, 74.15; H, 5.40; N, 3.50. $C_{24}H_{21}NO_2S$ requires C, 74.39; H, 5.46; N, 3.61%) δ_H ($CDCl_3$) 3.24 (1H, dd, J 13.6, 8.5Hz, $CHxCH_AH_B$), 3.30 (1H, dd, J 13.6, 7.4 Hz, $CHxCH_AH_B$), 3.81 (3H, s, OMe), 4.14 (1H, t, J ca. 8.0Hz, $CHxCH_AH_B$), 6.28 (1H, dd, J 3.3, 1.5Hz, thiophene H), 6.74 (1H, dd, J 5.2, 1.5Hz, thiophene H), 6.8-6.95 (5H, m), 7.1-7.3 (6H, m), and 8.39 (2H, br s, pyridine H_2,H_6).

The following Examples were prepared in a manner similar to compound of Example 2a).

b) **4-{2-(R)-[3-(4-Biphenyloxy)-4-methoxyphenyl)-2-phenyl]ethyl} pyridine**

From Intermediate 7a) (0.4g, 1.131mmol), anhydrous potassium carbonate (0.36g, 2.62mmol), 4-bromobiphenyl (0.4g, 1.70mmol) and copper (II) oxide (0.26g, 3.3mmol). Chromatography (SiO_2; EtOAc-hexane, 1:1 then 7:3) gave the title compound (0.383g) as a clear colourless foamy oil. (Found C, 83.40; H, 5.89; N, 3.03. $C_{32}H_{27}NO_2$ requires C, 83.92; H, 5.95; N, 3.06%). δ_H (300MHz; $CDCl_3$) 3.25 (1H, dd, J 13.6, 8.5Hz, pyridine CH_AH_B), 3.25 (1H, dd, J 13.6, 7.5Hz, pyridine CH_AH_B), 3.80 (3H, s, OCH_3), 4.16 (1H, t, C_6H_3CH), 6.85-7.0 (7H, m, ArH, pyridine H_3, H_5), 7,15-7.6 (12H, m, ArH) and 8.40 (2H, br s, pyridine H_2,H_6).

c) **4-[2-(R)-(4-Methoxy-3-phenyloxyphenyl)-2-phenylethyl]pyridine**

From Intermediate 7a) (0.4g, 1.31 mmol), anhydrous potassium carbonate (0.36g, 2.62mmol), bromobenzene (2.98g, 2.0ml, 19mmol) and copper (II) oxide (0.26g, 3.3mmol). Chromatography (SiO_2; EtOAc-hexane, 17:3) gave the title compound (0.433g) as a clear oil. (Found C, 81.45; H,

5.97; N, 3.48. $C_{26}H_{32}NO_2$ requires C, 81.86; H, 6.08; N, 3.67%). δ_H (300MHz; $CDCl_3$) 3.24 (1H, dd, J 13.6, 8.7Hz, pyridine $CH_A\underline{H}_B$), 3.29(1H, dd, J 13.6, 7.4Hz, pyridine $C\underline{H}_AH_B$), 3.78 (3H, s, $OC\underline{H}_3$), 4.14 (1H, t, J 7.9Hz, $CH_2C\underline{H}$), 6.80-6.94 (7H, m, Ar<u>H</u>, pyridine $\underline{H}_3$, $\underline{H}_5$), 7.00-7.06 (1H, m, Ar<u>H</u>), 7,15-7.3 (7H, m, Ar<u>H</u>) and 8.39 (2H, dd, J 4.5, 1.6Hz, pyridine $\underline{H}_2$,$\underline{H}_6$).

EXAMPLE 3

(2R)-4-[2-(3-((2RS)-exo-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)-2-phenylethyl]pyridine

Diethylazodicarboxylate (522mg, 3.0mmol) was added to a mixture of Intermediate 7a) (610mg, 2.0mmol), (±)-endo-2-norborneol (224mg, 2.0mmol), and triphenylphosphine (787mg, 3.0mmol) in THF (5ml) and the mixture heated to reflux for 40h. The reaction mixture was poured into saturated $NaHCO_3$ solution (10ml) and extracted with CH_2Cl_2 (2x25ml). The extract was dried (Na_2SO_4), concentrated *in vacuo*, and then subjected to chromatography (SiO_2; Et_2O) to afford the title compound (256mg) as a colourless oil. δ_H ($CDCl_3$) 1.0-1.75 (8H, m, norbornyl <u>H</u>'s), 2.2-2.4 (2H, br m, norbornyl <u>H</u>'s), 3.25-3.4 (2H, m, $CHC\underline{H}_2$), 3.77 (3H, s, O<u>Me</u>), 4.05 (1H, br d, J 5.6Hz, OC<u>H</u>), 4.14 (1H, t, J 7.9Hz, $C\underline{H}CH_2$), 6.6-6.8 (3H, m, C_6H_3), 6.92 (2H, ca. d, J 4.5Hz, pyridine $\underline{H}_3$, $\underline{H}_5$), 7.1-7.3 (5H, m, $C_6\underline{H}_5$), 8.38 (2H, ca.d., J 4.5Hz, pyridine $\underline{H}_2$,$\underline{H}_6$); m/z (EI) 399 (M^+, 8%), 307 (13), 305 (18), 213 (100), 152 (18), 95 (51), 93 (19), and 67 (37).

EXAMPLE 4

a) **3-(3-Cyclopentylidenyl-4-methoxyphenyl)pyridine hydrochloride**

To a solution of cyclopentyl triphenylphosphonium bromide (3.66g, 8.9mmol) in THF (50ml) was added dropwise n-BuLi (1.6M in hexane) (5.6ml, 9.0mmol) at 0°C. The red solution was stirred and left to warm up to RT for 1h then treated with a solution of Intermediate 8 (1.9g, 8.9mmol) in THF (25ml) at 0°C. After stirring for 1h at RT the reaction mixture was quenched with water (50ml) and extracted with CH_2Cl_2 (1 x 75, 1 x 50, 1 x 25ml). The extract was washed (brine), dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless syrup which crystallised to give a white solid. Purification by column chromatography [SiO_2; EtOAc] furnished the title compound free base (1.80g) as a white solid.

A portion of the free base (388mg) was treated with ethanolic HCl and diluted with a little Et_2O. The precipitate was decanted, washed (Et_2O) and dried *in vacuo* to furnish the title compound (420mg) as a pale yellow solid (Found: C, 71.56; H, 6.68; N, 4.74. $C_{18}H_{19}NO$. HCl requires C, 71.63; H, 6.68; N, 4.64%). δ_H (80MHz; $CDCl_3$) 1.6-1.9 (4H, br m, $CH_2(C\underline{H}_2)_2CH_2$), 2.4-2.65 (4H, br m, $C\underline{H}_2(CH_2)_2C\underline{H}_2$), 3.89 (3H, s, O$\underline{Me}$), 6.5-6.6 (1H, br m, $\underline{H}C{=}C$), 6.97 (1H, d, $\underline{J}$ 8.6Hz, Ar$\underline{H}$ ortho to OMe), 7.40 (1H, dd, $\underline{J}$ 8.6, 2.2Hz, Ar$\underline{H}$ para to C=C), 7.53 (1H, d $\underline{J}$ 2.2Hz, Ar$\underline{H}$ ortho to C=C), 7.9 (1H, dd, $\underline{J}$ 5.6, 8.3Hz, pyridine $\underline{H}_5$), 8.4-8.7 (2H, m, pyridine $\underline{H}_4$, $\underline{H}_6$) and 8.85 (1H, d, $\underline{J}$ 2.2Hz, pyridine $\underline{H}_2$).

b) **4-[2-(3-Cyclopentylidenylmethyl-4-methoxyphenyl)-2-phenylethyl]pyridine hyrochloride hemihydrate**

From n-BuLi (1,6M solution in hexane) (2.1ml, 3.55mmol, 1.06 equiv), cyclopentyltriphenylphosphonium bromide (1.43g, 3.46mmol, 1.1equiv) in THF (30ml) and Intermediate 18 (1.00g, 3.15mmol) in THF (20ml). Chromatography (SiO_2; 2% MeOH-CH_2Cl_2) afforded the title compound free base (420mg). δ_H ($CDCl_3$) 1.6-1.8 (4H, br m, $CH_2(C\underline{H}_2)_2CH_2$), 2.2-2.35 (2H, br m, $C\underline{H}(CH_2)_2C\underline{H}$), 2.4-2.55 (2H, br m, $C\underline{H}(CH_2)_2C\underline{H}$), 3.22 (2H, d, $\underline{J}$ 7.8Hz, $CHC\underline{H}_2$ pyridine), 3.78 (3H, s, O$\underline{Me}$), 4.17 (1H, t, $\underline{J}$ 7.8Hz, $C\underline{H}CH_2$ pyridine), 6.51 (1H, ca. t, $\underline{J}$ 2.2Hz, $\underline{H}C{=}CCH_2$), 6.72 (1H, d, $\underline{J}$ 8.4Hz, Ar$\underline{H}$ ortho to OMe), 6.85-7.0 (3H, m, $\underline{H}$ of C_6H_3 + pyridine $\underline{H}_3$, $\underline{H}_5$), 7.1-7.3 (6H, m, $C_6\underline{H}_5$+ $\underline{H}$ of C_6H_3) and 8.38 (2H, ca. d, $\underline{J}$ 5.7Hz, pyridine $\underline{H}_2$, $\underline{H}_6$).

The base (420mg) was dissolved in Et_2O (5 ml) and treated dropwise with ethanolic HCl. The precipitated product was collected by filtration and dried *in vacuo* to afford the title compound as a white solid (Found: C, 75.23; H, 6.72; N, 3.11; $C_{26}H_{28}NO$. $0.5H_2O$ requires C, 75.25; H, 7.04; N, 3.38%). δ_H ($CDCl_3$) 1.6-1.8 (4H, br m, $CH_2(C\underline{H}_2)_2CH_2$), 2.2-2.35 (2H, br m, $C\underline{H}(CH_2)_2C\underline{H}$), 2.4-2.55 (2H, br m, $C\underline{H}(CH_2)_2C\underline{H}$), 3.59 (2H, d, $\underline{J}$ 8.0Hz, $CHC\underline{H}_2$ pyridine), 3.80 (3H, s, O$\underline{Me}$),

4.18 (1H, t, $\underline{J}$ 8.0Hz, $C\underline{H}CH_2$ pyridine), 6.51 (1H, ca. t, $\underline{J}$ 2.0Hz, $C\underline{H}{=}CCH_2$), 6.73 (1H, d, $\underline{J}$ 8.4Hz, Ar$\underline{H}$ ortho to OMe), 6.87 (1H, dd, $\underline{J}$ 2.2, 8.4Hz, Ar$\underline{H}$ para to olefin), 7.1-7.45 (6H, m, $C_6\underline{H}_5$ + Ar$\underline{H}$ ortho to olefin), 7.46 (2H, ca. d, $\underline{J}$ ca. 6.4Hz, pyridine $\underline{H}_3$, $\underline{H}_5$), and 8.50 (2H, ca. d, $\underline{J}$ ca.

6.4Hz, pyridine $\underline{H}_2$, $\underline{H}_6$); $\underline{m/z}$ (ESI) 370 ($\underline{M}^+$+ 1-HCl, 18%), 369 ($\underline{M}^+$-HCl, 95), 277 (100), 178 (55), 165 (75), and 152 (45).

c) **4-[2-(3-Cyclohexylidenylmethyl-4-methoxyphenyl)-2-phenyl-ethyl]pyridine hydrochloride**

From Intermediate 18 (1.00g, 3.15mmol), cyclohexyltriphenylphosphonium bromide (1.47g, 3.46mmol, 1.1 equiv) and n-BuLi (1.6 M solution in hexane) (2.1ml, 3.36mmol, 1.07 equiv). The crude product was subjected to chromatography (SiO_2; 2% MeOH-CH_2Cl_2) to afford the title compound free base (1.07g).

A portion of the free base (400mg) was dissolved in Et_2O (5ml) and treated with ethanolic HCl to afford the title compound as a white solid (Found: C, 77.32; H, 7.15; N, 3.24. $C_{27}H_{30}ClNO$ requires C, 77.21; H, 7.20; N, 3.34%). δ_H ($CDCl_3$) 1.4-1.75 (6H, br m, $CH_2(C\underline{H}_2)_3CH_2$), 2.0-2.1 (2H, br m, $C\underline{H}(CH_2)_3C\underline{H}$), 2.2-2.3 (2H, br m, $C\underline{H}(CH_2)_3C\underline{H}$), 3.58(2H, d, $\underline{J}$ 8.0Hz, $CHC\underline{H}_2$ pyridine), 3.78 (3H, s, O$\underline{Me}$), 4.18 (1H, t, $\underline{J}$ 8.0Hz, $C\underline{H}CH_2$ pyridine), 6.15 (1H, ca. s, $\underline{H}C$=CH_2), 6.73 (1H, d, $\underline{J}$ 9.0Hz, Ar$\underline{H}$ ortho to OMe), 6.85-6.95 (2H, m, Ar$\underline{H}$), 7.1-7.35 (5H, m, Ar$\underline{H}$), 7.46 (2H, d, $\underline{J}$ 5.8Hz, pyridine $\underline{H}_3$, $\underline{H}_5$), and 8.50 (2H, d. $\underline{J}$ 5.8Hz, pyridine $\underline{H}_2$, $\underline{H}_6$); $\underline{m/z}$ (ESI) 384 ($\underline{M}^+$+ 1-HCl, 37%), 383 ($\underline{M}^+$-HCl, 85), 291 (100), 178 (32), 165 (50), 152 (28) and 91 (33).

d) **4-{2(R)-[3-(Phenyl-1,3-butedienyl)-4-methoxyphenyl]-2-phenylethyl}pyridine**

From n-BuLi (1.6M solution in hexane) (1.2ml, 2.93mmol, 1.05equiv). cinnamyltriphenylphosphonium bromide (930.6mg, 2.02mmol) and Intermediate 9 (583.9mg, 1.84mmol). Chromatography (SiO_2; EtOAc-hexane, 1:1) gave the title compound.

EXAMPLE 5

a) **3-(3-Cyclopentylmethyl-4-methoxyphenyl) pyridine hydrochloride**

The compound of Example 4a) (485mg) was hydrogenated over the weekend in EtOH (25ml) in the presence of 5% Pd/C (50mg). The reaction mixture was filtered through Celite and concentrated *in vacuo* to give the title compound free base (464mg) as a colourless oil.

The free base was dissolved in warm ethanolic HCl, precipitated with Et_2O, decanted and dried *in vacuo* to yield the title compound (485mg) as a white solid. (Found: C, 70.98; H, 7.31; N, 4.62. $C_{18}H_{21}NO$. HCl requires C, 71.16; H, 7.30; N, 4.61%). δ_H (80MHz; $CDCl_3$) 1.5-1.8 ((H, v.br m, cyclopentyl H's), 2.67 (2H, d, J 6.8Hz,CH_2 cyclopentyl), 3.87 (3H, s, OMe), 6.95 (1H, d, J 8.0Hz, ArH ortho to OMe), 7.35-7.50 (2H, m, 2xArH meta to OMe), 7.8-8.0 (1H, m, pyridine H_5), 8.4-8.65 (2H, m, pyridine H) and 8.87 (1H, ~d, J 2.0 Hz, pyridine H_2) .

The following compound was prepared in a manner similar to the compound of Example 5a)

b) **4-{2-[4-Methoxy-3-(5-phenylpentyloxy)phenylethyl}pyridine**

From the compound of Example 1c) (0.534g, 1.43mmol) and 5% Pd/C catalyst (40mg). Chromatography (SiO_2; EtOAc-hexane, 3:1) gave a clear colourless oil which solidified to give the title compound (0.45g) as a white amorphous solid. m.p. 59-62°C. (Found C, 79.63; H, 7.79; N, 3.57. $C_{25}H_{29}NO_2$ requires C, 79.96; H, 7.78; N, 3.73%) δ_H (300MHz; $CDCl_3$) 1.4-1.9 (6H, br m, $(CH_2)_3$), 2.65 (2H, t, J 7.7Hz, $ArCH_2$), 2.83-2.91 (4H, m, $(CH_2)_2$), 3.83 (3H, s, OCH_3) , 3.94 (2H, t, J 6.8Hz, OCH_2), 6.63 (1H, d, J 2.0Hz, ArH_2), 6.66 (1H, dd, J 8.0, 2.0Hz, ArH_6), 6.78 (1H, d, J 8.1Hz, ArH_4), 7.06 (2H, dd, J 4.4, 1.6Hz, pyridine H_3, H_5), 7.15-7.3 (5H, m, ArH), and 8.47 (2H, dd, J 4.4, 1.6Hz, pyridine H_2, H_6).

c) **4-[2-(4-Methoxy-3-butylphenyl)-2-phenylethyl]pyridine hydrochloride**

From the compound of Example 4d). Chromatography (SiO_2; EtOAc-hexane, 1:9) gave the title compound free base as a colourless oil.
The free base was treated with ethanolic HCl to give the title compound as an off-white solid. (Found C, 78.13; H, 6.98; N, 3.02 $C_{30}H_{32}NOCl$ requires C, 78.67; H, 7.04; N, 3.06%). δ_H ($CDCl_3$) 1.55 (4H, m, $CH_2(CH_2)CH_2$), 2.60 (4H, m, $CH_2(CH_2)_2CH_2$), 3.55 (2H, d, pyridine (CH_2), 3.75 (3H, s, OCH_3), 4.15 (1H, t, ArCH), 6.70 (m, ArH), 6.90 (2H, m, ArH), 7.10-7.30 (10H, m, $2xC_6H_5$), 7.4 (2H, d, ArH) and 8.55 (2H, d, ArH).

EXAMPLE 6

Methyl 3-[Cyclop ntylid nyl-4-meth xyphenyl]propenoate

A mixture of trimethylphosphonoacetate (2.7g, 14.8mmol) and Intermediate 13 (3.00g, 13.9 mmol) in MeOH (30ml) was added to a solution of sodium methoxide [prepared from sodium (0.4g, 17.4mmol) in MeOH (50ml) at RT]. The reaction mixture was stirred at RT overnight then the crystalline product collected by filtration, washed with MeOH (2 x 10ml), and dried *in vacuo* to afford the title compound (2.70g) as a white solid (Found: C, 74.73; H, 7.43 $C_{17}H_{20}O_3$ requires: C, 74.97; H, 7.40%); δ_H (80MHz; $CDCl_3$) 1.5-1.8 (4H, br m, $CH_2(C\underline{H_2})_2$), 2.4-2.6 (4H, br m, $C\underline{H_2}(CH_2)_2C\underline{H_2}$), 3.77 (3H, s, O<u>Me</u>), 6.25 (1H, d, J 15.8Hz, C<u>H</u>=CH), 6.45-6.55 (1H, br m, C<u>H</u>=CCH_2), 6.80 (1H, d, J 8.7Hz, ArH ortho to OMe), 7.28 (1H, dd, J 8.7, 2.6Hz, ArH para to cyclopentylidene), 7.48 (1H, d, J 2.6Hz, ArH ortho to cyclopentylidene), and 7.61 (1H, d, J 15.8 Hz, CH=C<u>H</u>); m/z (EI) 273 (M^+ + 1, 18%), 272 (100), 241 (11), 239 (11), 225 (11), 205 (19), 192 (17), 175 (11), 161 (17), and 115 (18).

The activity and selectivity of compounds according to the invention was demonstrated in the following tests. In these tests the abbreviation FMLP represents the peptide N-formyl-met-leu-phe.

1. **Isolated Enzyme**

The potency and selectivity of the compounds of the invention was determined using distinct PDE isoenzymes as follows:

i. PDE I, rabbit heart
ii. PDE II, rabbit heart
iii. PDE III, rabbit heart, Jurkat cells
iv. PDE IV, HL60 cells, rabbit brain, rabbit kidney and human recombinant PDE IV
v. PDE V, rabbit lung, guinea pig lung

A gene encoding human PDE IV has been cloned from human monocytes (*Livi, et al., 1990, Molecular and Cellular Biology, 10, 2678*). Using similar procedures we have cloned human PDE IV

genes from a number of sources including eosinophils, neutrophils, lymphocytes, monocytes, brain and neuronal tissues. These genes have been transfected into yeast using an inducible vector and various recombinant proteins have been expressed which have the biochemical characteristics of PDE IV (*Beavo and Reifsnyder, 1990, TIPS, 11, 150*). These recombinant enzymes, particularly the human eosinophil recombinant PDE IV, have been used as the basis of a screen for potent, selective PDE IV inhibitors.

The enzymes were purified to isoenzyme homogeneity using standard chromatographic techniques.

Phosphodiesterase activity was assayed as follows. The reaction was conducted in 150μl of standard mixture containing (final concentrations): 50mM 2-[[tris(hydroxymethyl)methyl]amino]-1-ethanesulphonic acid (TES) -NaOH buffer (pH 7.5), 10mM $MgCl_2$, 0.1μM [^{3}H]-cAMP and vehicle or various concentrations of the test compounds. The reaction was initiated by addition of enzyme and conducted at 30^{o}C for between 5 to 30 min. The reaction was terminated by addition of 50μl 2% trifluoroacetic acid containing [^{14}C]-5'AMP for determining recovery of the product. An aliquot of the sample was then applied to a column of neutral alumina and the [^{3}H]-cAMP eluted with 10ml 0.1 TES-NaOH buffer (pH8). The [^{3}H]-5'-AMP product was eluted with 2ml 2M NaOH into a scintillation vial containing 10ml of scintillation cocktail. Recovery of [^{3}H]-5'AMP was determined using the [^{14}C]-5'AMP and all assays were conducted in the linear range of the reaction.

Compounds according to the invention such as compounds of the Examples herein cause a concentration-dependent inhibition of recombinant PDE IV at 0.1 - 1000nM with little or no activity against PDE I, II, III or V at concentrations up to 100μM.

2. **The Elevation of cAMP in Leukocytes**

The effect of compounds of the invention on intracellular cAMP was investigated using human neutrophils or guinea pig eosinophils.

Human neutrophils were separated from peripheral blood, incubated with dihydrocytochalasin B and the test compound for 10 min and then stimulated with FMLP. Guinea pig eosinophils were harvested by peritoneal lavage of animals previously treated with intra-peritoneal injections of human serum. Eosinophils were separated from the peritoneal exudate and incubated with isoprenaline and test compound. With both cell types, suspensions were centrifuged at the end of the incubation, the cell pellets were resuspended in buffer and boiled for 10 min prior to measurement of cAMP by specific radioimmunoassay (DuPont).

The most potent compounds according to the Examples induced a concentration -dependent elevation of cAMP in neutrophils and/or eosinophils at concentrations of 0.1nM to 1μM.

3. <u>Suppression of Leukocyte Function</u>

Compounds of the invention were investigated for their effects on superoxide generation, chemotaxis and adhesion of neutrophils and eosinophils. Isolated leukocytes were incubated with dihydrocyto-chalasin B for superoxide generation only and test compound prior to stimulation with FMLP. The most potent compounds of the Examples caused a concentration-dependent inhibition of superoxide generation, chemotaxis and adhesion at concentrations of 0.1nM to 1μM.

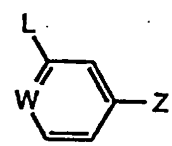
Lipopolysaccharide (LPS)-induced synthesis of tumour necrosis factor (TNF) by human peripheral blood monocytes (PBM) is inhibited by compounds of the Examples at concentrations of 0.01nM to 10μM.

4. <u>Adverse Effects</u>

In general, in our tests, compounds of the invention have had no observed toxic effects when administered to animals at pharmacologically effect doses.

CLAIMS

1. A compound of formula (1)



(1)

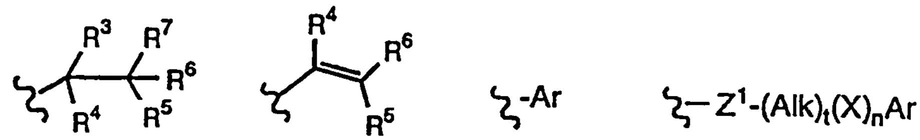
wherein

=W- is (1) =C(Y)- where Y is a halogen atom, or an alkyl or $-XR^a$ group where X is -O-, $-S(O)_m-$ [where m is zero or an integer of value 1 or 2], or $-N(R^b)-$ [where R^b is a hydrogen atom or an optionally substituted alkyl group] and R^a is a hydrogen atom or an optionally substituted alkyl group or, (2) =N-;

L is (1) a $-C(R)=C(R^1)(R^2)$ or $[-CH(R)]_nCH(R^1)(R^2)$ group where R is a hydrogen or a fluorine atom or a methyl group, and R^1 and R^2, which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, $-CO_2R^8$ [where R^8 is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group], $-CONR^9R^{10}$ [where R^9 and R^{10}, which may be the same or different are defined for R^8], $-CSNR^9R^{10}$,-CN or $-NO_2$ group, or R^1 and R^2, together with the C atom to which they are attached are linked to form an optionally substituted cycloalkyl, cycloalkenyl or heterocycloaliphatic group and n is zero or the integer 1; or is (2) $-(X^a)_nAlk'Ar'$, or $-Alk'X^aAr'$ where X^a is a group X, Ar' is an optionally substituted heterocycloaliphatic, or an optionally substituted monocylic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms, Alk' is an optionally substituted straight or branched alkylene, alkenylene or alkynylene chain optionally interrupted by one or more L^1 atoms or groups [where L^1 is a linker atom or group] and n is zero or the integer 1; or is (3) X^aR' where R'

Ar' or is an optionally substituted polycycloalkyl or polycycloalkenyl group optionally containing one or more -O-, or -S- atoms or $-N(R^b)-$ groups;

Z is a group (A), (B), (C) or (D):



(A), (B), (C), or (D)

wherein

Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

Z^1 is a group $-NR^{12}C(O)-$ [where R^{12} is a hydrogen atom or an optionally substituted alkyl or $(Alk)_tAr$ group], $-C(O)NR^{12}-$, $-NR^{12}C(S)-$, $-C(S)NR^{12}-$, $-C{\equiv}C-$, $-NR^{12}SO_2-$, or $-SO_2NR^{12}-$;

Alk is an optionally substituted straight or branched alkyl chain optionally interrupted by an atom or group X;

t is zero or an integer of value 1, 2 or 3;

R^3 is a hydrogen or a fluorine atom or an optionally substituted straight or branched alkyl group or an OR^{11} group [where R^{11} is a hydrogen atom or an optionally substituted alkyl, alkenyl, alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group];

R^4 is a hydrogen atom or an optionally substituted alkyl, $-CO_2R^8$, $-CSNR^9R^{10}$, -CN, $-CH_2CN$, or $-(CH_2)_tAr$ group where t is zero or an integer of value 1, 2 or 3 and Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms, provided that when L is a group of type (2) or (3) above then Z is a group of type (A) or type (B) in which R^4 is a $-(CH_2)_tAr$ group;

R^5 is a group $-(CH_2)_tAr$;

R^6 is a hydrogen or a fluorine atom, or an optionally substituted alkyl or $-CO_2R^8$, $-CONR^9R^{10}$, $-CSNR^9R^{10}$, -CN or $-CH_2CN$ group;

R^7 is a hydrogen or a fluorine atom, an optionally substituted straight or branched alkyl group, or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, alkoxyalkyl,

alkanoyl, formyl, carboxamido or thiocarboxamido group; and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

2. A compound according to Claim 1 wherein W is a $=C(XR^a)-$ group.

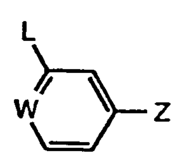
3. A compound according to Claim 1 or Claim 2 wherein L is a $-C(R)=C(R^1)(R^2)$ group in which R^1 and R^2, together with the C atom to which they are attached are linked to form a cycloalkyl group.

4. A compound according to Claims 1 to 3 wherein Z is a group (A) or (B), in which R^3, R^6 and R^7 is each a hydrogen atom, R^4 is an aryl group and R^5 is a heteroaryl group.

5. A compound according to Claim 4 wherein R^4 is an optionally substituted phenyl group and R^5 is an optionally substituted pyridyl group.

6. A compound which is:
4-{2-[4-Methoxy-3-(phenylpentyloxy)phenyl]-2-phenylethyl}pyridine;
4-[2-(4-Methoxy-3-(3-thienyloxy)phenyl)-2-phenylethyl]pyridine;
4-{2-[3-(4-Biphenyloxy)-4-methoxyphenyl)-2-phenyl]ethyl}pyridine;
4-[2-(3-((2RS)-exo-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)-2-phenylethyl]pyridine;
3-(3-Cyclopentylidenyl-4-methoxyphenyl)pyridine;
the resolved enantiomer; and the salts, solvates, hydrates, prodrugs and n-oxides thereof

7. A pharmaceutical composition comprising a compound of formula (1)



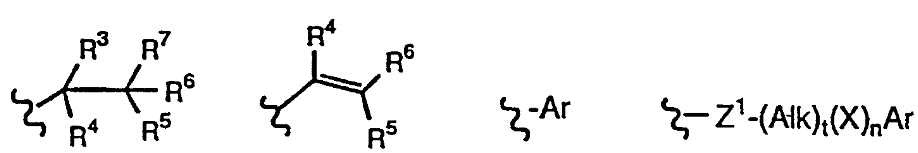
(1)

wherein

=W- is (1) =C(Y)- where Y is a halogen atom, or an alkyl or $-XR^a$ group where X is -O-, $-S(O)_m-$ [where m is zero or an integer of value 1 or 2], or $-N(R^b)-$ [where R^b is a hydrogen atom or an optionally substituted alkyl group] and R^a is a hydrogen atom or an optionally substituted alkyl group or, (2) =N-;

L is (1) a $-C(R)=C(R^1)(R^2)$ or $[-CH(R)]_nCH(R^1)(R^2)$ group where R is a hydrogen or a fluorine atom or a methyl group, and R^1 and R^2, which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, $-CO_2R^8$ [where R^8 is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group], $-CONR^9R^{10}$ [where R^9 and R^{10}, which may be the same or different are defined for R^8], $-CSNR^9R^{10}$,-CN or $-NO_2$ group, or R^1 and R^2, together with the C atom to which they are attached are linked to form an optionally substituted cycloalkyl, cycloalkenyl or heterocycloaliphatic group and n is zero or the integer 1; or is (2) $-(X^a)_n$Alk'Ar', or $-Alk'X^aAr'$ where X^a is a group X, Ar' is an optionally substituted heterocycloaliphatic, or an optionally substituted monocylic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms, Alk' is an optionally substituted straight or branched alkylene, alkenylene or alkynylene chain optionally interrupted by one or more L^1 atoms or groups [where L^1 is a linker atom or group] and n is zero or the integer 1; or is (3) X^aR' where R' is Ar' or is an optionally substituted polycycloalkyl or polycycloalkenyl group optionally containing one or more -O-, or -S- atoms or $-N(R^b)-$ groups;

Z is a group (A), (B), (C) or (D):



(A), (B), (C), or (D)

wherein

Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

Z^1 is a group $-NR^{12}C(O)-$ [where R^{12} is a hydrogen atom or an optionally substituted alkyl or $(Alk)_tAr$ group], $-C(O)NR^{12}-$, $-NR^{12}C(S)-$, $-C(S)NR^{12}-$, $-C{\equiv}C-$, $-NR^{12}SO_2-$, or $-SO_2NR^{12}-$;

Alk is an optionally substituted straight or branched alkyl chain optionally interrupted by an atom or group X;

t is zero or an integer of value 1, 2 or 3;

R^3 is a hydrogen or a fluorine atom or an optionally substituted straight or branched alkyl group or an OR^{11} group [where R^{11} is a hydrogen atom or an optionally substituted alkyl, alkenyl, alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group];

R^4 is a hydrogen atom or an optionally substituted alkyl, $-CO_2R^8$, $-CSNR^9R^{10}$, -CN, $-CH_2CN$, or $-(CH_2)_tAr$ group where t is zero or an integer of value 1, 2 or 3 and Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms, provided that when L is a group of type (2) or (3) above then Z is a group of type (A) or type (B) in which R^4 is a $-(CH_2)_tAr$ group;

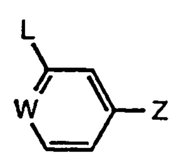
R^5 is a group $-(CH_2)_tAr$;

R^6 is a hydrogen or a fluorine atom, or an optionally substituted alkyl or $-CO_2R^8$, $-CONR^9R^{10}$, $-CSNR^9R^{10}$, -CN or $-CH_2CN$ group;

R^7 is a hydrogen or a fluorine atom, an optionally substituted straight or branched alkyl group, or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group; and the salts, solvates, hydrates, prodrugs and N-oxides thereof;

together with one or more pharmaceutically acceptable carriers, excipients or diluents.

8. A process for the preparation of a compound of formula (1)



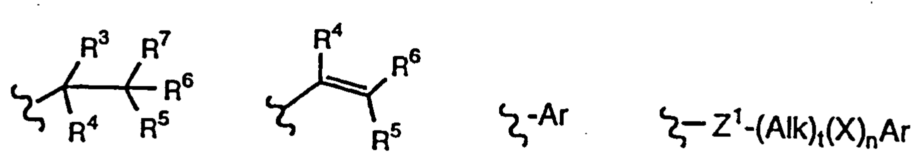
(1)

wherein

=W- is (1) =C(Y)- where Y is a halogen atom, or an alkyl or $-XR^a$ group where X is -O-, $-S(O)_m-$ [where m is zero or an integer of value 1 or 2], or $-N(R^b)-$ [where R^b is a hydrogen atom or an optionally substituted alkyl group] and R^a is a hydrogen atom or an optionally substituted alkyl group or, (2) =N-;

L is (1) a $-C(R)=C(R^1)(R^2)$ or $[-CH(R)]_nCH(R^1)(R^2)$ group where R is a hydrogen or a fluorine atom or a methyl group, and R^1 and R^2, which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, $-CO_2R^8$ [where R^8 is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group], $-CONR^9R^{10}$ [where R^9 and R^{10}, which may be the same or different are defined for R^8], $-CSNR^9R^{10}$,-CN or $-NO_2$ group, or R^1 and R^2, together with the C atom to which they are attached are linked to form an optionally substituted cycloalkyl, cycloalkenyl or heterocycloaliphatic group and n is zero or the integer 1; or is (2) $-(X^a)_nAlk'Ar'$, or $-Alk'X^aAr'$ where X^a is a group X, Ar' is an optionally substituted heterocycloaliphatic, or an optionally substituted monocylic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms, Alk' is an optionally substituted straight or branched alkylene, alkenylene or alkynylene chain optionally interrupted by one or more L^1 atoms or groups [where L^1 is a linker atom or group] and n is zero or the integer 1; or is (3) X^aR' where R' is Ar' or is an optionally substituted polycycloalkyl or polycycloalkenyl group optionally containing one or more -O-, or -S- atoms or $-N(R^b)-$ groups;

Z is a group (A), (B), (C) or (D):



(A), (B), (C), or (D)

wherein

Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

Z^1 is a group $-NR^{12}C(O)-$ [where R^{12} is a hydrogen atom or an optionally substituted alkyl or $(Alk)_tAr$ group], $-C(O)NR^{12}-$, $-NR^{12}C(S)-$, $-C(S)NR^{12}-$, $-C{\equiv}C-$, $-NR^{12}SO_2-$, or $-SO_2NR^{12}-$;

Alk is an optionally substituted straight or branched alkyl chain optionally interrupted by an atom or group X;

t is zero or an integer of value 1, 2 or 3;

R^3 is a hydrogen or a fluorine atom or an optionally substituted straight or branched alkyl group or an OR^{11} group [where R^{11} is a hydrogen atom or an optionally substituted alkyl, alkenyl, alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group];

R^4 is a hydrogen atom or an optionally substituted alkyl, $-CO_2R^8$, $-CSNR^9R^{10}$, -CN, $-CH_2CN$, or $-(CH_2)_tAr$ group where t is zero or an integer of value 1, 2 or 3 and Ar is a monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms, provided that when L is a group of type (2) or (3) above then Z is a group of type (A) or type (B) in which R^4 is a $-(CH_2)_tAr$ group;

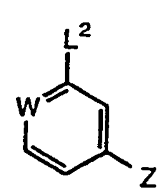
R^5 is a group $-(CH_2)_tAr$;

R^6 is a hydrogen or a fluorine atom, or an optionally substituted alkyl or $-CO_2R^8$, $-CONR^9R^{10}$, $-CSNR^9R^{10}$, -CN or $-CH_2CN$ group;

R^7 is a hydrogen or a fluorine atom, an optionally substituted straight or branched alkyl group, or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group; and the salts, solvates, hydrates, prodrugs and N-oxides thereof;

which comprises in a final step:

a) coupling a compound of formula (3)

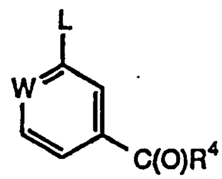


(3)

i) where L^2 is a group X^aH with a reagent $L^3Alk'Ar'$, or L^3R' in which L^3 is a leaving group; or

ii) where L^2 is a group $-Alk'L^3$ with a reagent $Ar'X^aH$;

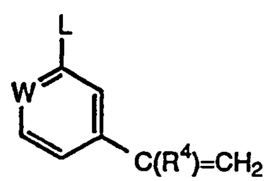
b) reacting a compound of formula (12)



(12)

where R^4 is a hydrogen atom, or an alkyl or $-(CH_2)_tAr$ group with a phosphonate ester to give a compound of formula (1) wherein Z is a group (B);

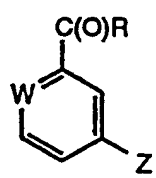
c) coupling a compound of formula (18)



(18)

with an organopalladium compound to give a compound of formula (1) wherein Z is a group (B);

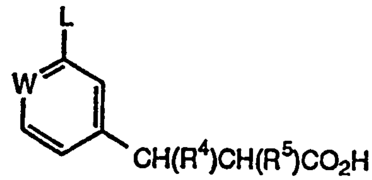
d) reacting a compound of formula (19)



(19)

with an organometallic reagent followed by dehydration of the corresponding alcohol to give a compound of formula (1) wherein L is a group $-C(R)=CH(R^1)$;

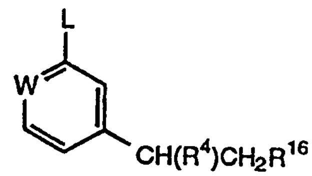
e) decarboxylating an acid of formula (21)



(21)

to give a compound of formula (1) wherein R^3, R^6 and R^7 is each a hydrogen atom;

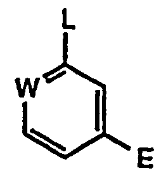
f) cyclisation of a compound of formula (23)



(23)

where R^{16} is a carboxylic acid (CO_2H) or a reactive derivative thereof; or a nitrile (-CN) or an imine salt with a bifunctional reagent $W^1R^{5a}W^2$ and, where necessary, a compound $R^{5b}W^3$ [where W^1, W^2 and W^3, which may be the same or different, is each a reactive functional group or a protected derivative thereof; and R^{5a} and R^{5b} are components of the heteroaryl group R^5 such that when added together with W^1, W^2 and W^3 to the group R^{16} in compounds of formula (19) the resulting group $-RW^1R^{5a}W^2$ or $-RW^1R^{5a}W^2R^{5b}W^3$ constitutes the heteroaryl group R^5]; to give a compound of formula (1) wherein R^3, R^6 and R^7 is each a hydrogen atom and R^5 is a heteroaryl group to give a compound of formula (1) wherein R^3, R^6 and R^7 is each a hydrogen atom and R^5 is a heteroaryl group;

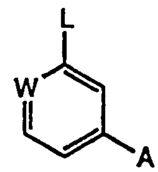
g) coupling a compound of formula (25)



(25)

where E is a boronic acid $-B(OH)_2$ or a tin reagent $Sn(R)_3$, in which R is an alkyl group with a reagent $Z-L^4$, where L^4 is a leaving group, in the presence of a complex metal catalyst;
to give a compound of formula (1) wherein Z is a group (C);

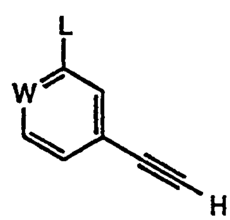
h) coupling a compound of formula (26)



(26)

where A is a $-CO_2H$ or $-NHR^{12}$ group, or an active derivative thereof with a compound $R^{12}NH(Alk)_t(X_n)Ar$ or $Ar(X)_nAlk)_tCO_2H$ or an active derivative thereof to give a compound of formula (1) wherein Z is a group (D) in which $-Z^1$ is $-NR^{12}C(O)-$ or $-C(O)NR^{12}-$;

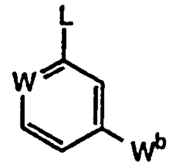
i) reacting a compound of formula (29)



(29)

with a reagent $Ar(X)_n(Alk)_tL^5$ in which L^5 is a leaving group to give a compound of formula (1) wherein Z^1 is a -C≡C-chain;

j) reacting a compound of formula (30)

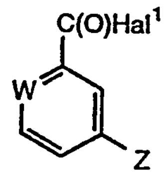


(30)

where (i) W^b is a $-NHR^{12}$ group with a compound $Ar(X)_n(Alk)_tSO_2Hal$ (where Hal is a halogen atom); or

(ii) W^b is a $-SO_2Hal$ group with a compound $Ar(X)_n(Alk)_tNHR^{12}$ to give a compound of formula (1) wherein Z^1 is a $-NR^{12}SO_2-$ or $-SO_2NR^{12}-$ group;

k) reacting a compound of formula (31)



(31)

where Hal^1 is a halogen atom

where a diazoalkane to give a compound of formula (1) where L is a $-CH(R^1)(R^2)$group in which R^2 is a $-CO_2H$ group; or

l) interconverting a compound of formula (1) to another compound of formula (1).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/01461

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/30 A61K31/44 C07D409/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO,A,94 14800 (CELLTECH LIMITED) 7 July 1994 see intermediates 7a, 7c, 7d, 7e ---	1,2,4,5, 8
X,P	WO,A,94 14742 (CELLTECH LIMITED) 7 July 1994 cited in the application see the whole document ---	1-8
X	WO,A,94 10118 (CELLTECH LIMITED) 11 May 1994 see claims 1-11; example 3a ---	1-8
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 1995	- 5. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TRENDS IN PHARMACOLOGICAL SCIENCES, vol.11, 1990, CAMBRIDGE GB pages 150 - 155 J.A. BEAVO ET AL. 'Primary sequence of cyclic nucleotide phosphodiesterase isozymes and the design of selective inhibitors.' cited in the application see the whole document ---	1,7
A	TRENDS IN PHARMACOLOGICAL SCIENCES, vol.12, 1991, CAMBRIDGE GB pages 19 - 27 C.D NICHOLSON ET AL. 'Different modulation of tissue function and therapeutic optential of selective inhibitors of cyclic nucleotide phosphodiesterase isoenzymes.' cited in the application see the whole document -----	1,7

INTERNATIONAL SEARCH REPORT	International application No. PCT/GB95/01461

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The subject matter of the present claims is so broad that a complete search is not possible on economic grounds (PCT Search Guidelines III, 3.6 and 3.7). Therefore the search has been based on the examples and the claims as indicated. Claims searched incompletely:1,3,7,8.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 95/01461

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9414800	07-07-94	AU-B-	5709394	19-07-94
		EP-A-	0626957	07-12-94
		JP-T-	7504687	25-05-95
WO-A-9414742	07-07-94	AU-B-	5709294	19-07-94
		CA-A-	2129039	07-07-94
		CN-A-	1092064	14-09-94
		CZ-A-	9402034	15-12-94
		EP-A-	0626939	07-12-94
		FI-A-	943856	22-08-94
		GB-A-	2279075	21-12-94
		JP-T-	7504442	18-05-95
		NO-A-	943091	21-10-94
		PL-A-	304892	09-01-95
WO-A-9410118	11-05-94	AU-B-	5340894	24-05-94
		CA-A-	2126072	11-05-94
		EP-A-	0618889	12-10-94
		JP-T-	7502762	23-03-95